Appeal No. 05-1184
(Serial No. 09/674,002)

In the

United States Court of Appeals

for the

Federal Circuit

IN RE MARTIN BILLGER and MIKAEL BRULLS

Appeal from the United States Patent and Trademark Office,
Board of Patent Appeals and Interferences.

BRIEF OF APPELLANTS MARTIN BILLGER & MIKAEL BRULLS (corrected)

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CERTIFICATE OF INTEREST

Counsel for Appellants Martin Billger and Mikael Brulls certifies the following:

1. The full name of every party represented by me is:

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2. The name of the real party in interest represented by me is:

NPS Allelix Corp.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

NPS Pharmaceuticals, Inc.

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4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

I. STATEMENT OF RELATED CASES

No appeal in or from the same proceeding was previously before this Court. Counsel knows of no cases pending in this or any other court that will directly affect or be directly affected by this Court's decision in this appeal.

II. JURISDICTIONAL STATEMENT

This is an appeal from the United States Patent and Trademark Office Board of Patent Appeals and Interferences ("Board") decision dated September 30, 2004, which affirmed the Examiner's rejection of claims 1-7, 9, 12, 17, 18, 20-28, and 31-36 of U.S. Patent Application Serial No. 09/674,002. [A1-13] The Board decision is final and appealable. The Board had jurisdiction under 35 U.S.C. § 134. This Court has jurisdiction under 28 U.S.C. § 1295(a)(4)(A). The Notice of Appeal to this Court was timely filed on November 30, 2004. [A313] See 35 U.S.C. § 142; 37 C.F.R. § 1.301.

III. STATEMENT OF THE ISSUES

This appeal raises the following issues:

1. Does the Board's decision to disregard the explicit teaching away from the claimed parathyroid hormone invention that is set forth in Martindale 1989, based only on the observation that a later edition of Martindale contains a shorter entry for parathyroid hormone that omits the explicit teaching away,

lack substantial evidence support where there is no evidence that the revisions to Martindale reflected a change in the state of the art?

2. Given that the Endo reference is limited to stabilizing lyophilized preparations of parathyroid hormone, and fails to teach or suggest that sodium chloride could be used to stabilize liquid parathyroid hormone formulations, does the Board's finding that Endo supports the obviousness of the claimed stable, liquid parathyroid hormone formulations lack substantial evidence support?

3. Did the Board lack substantial evidence to find that Endo contravenes the teachings in Canadian Patent Application No. 2,234,724, which specifically warns against using sodium chloride in liquid parathyroid hormone formulations because of dimer formation, where Endo does not even consider the stability of liquid formulations of parathyroid hormone, much less address whether dimers would form in a liquid parathyroid hormone formulation that includes sodium chloride?

4. Should the Board decision be reversed because the cited art does not provide a motivation to combine the references with an expectation of success in achieving the claimed invention, but instead teaches away from Applicants' approach?

IV. STATEMENT OF THE CASE

This is an appeal from the Board decision affirming the Examiner's rejection of claims 1-7, 9, 12, 17, 18, 20-28, and 31-36 of U.S. Patent Application Serial No. 09/674,002 as unpatentable under 35 U.S.C. § 103(a). [A1-13] The sole rejection before the Board and on appeal is the obviousness rejection based on U.S. Patent No. 5,563,122 to Endo ("Endo") and U.S. Patent No. 5,496,801 to Holthuis ("Holthuis"). [A2]

U.S. Patent Application No. 09/674,002 names Applicants Martin Billger and Mikael Brulls as inventors. [A200] The application is the U.S. national stage application of International Patent Application PCT/CA99/00376, filed on April 26, 1999. [A200] The application also claims the benefit of Swedish Application No. 9801495-4, filed April 28, 1998. [A200]

V. STATEMENT OF FACTS

A. SUMMARY OF THE CLAIMED INVENTION

The invention on appeal relates to formulations of human parathyroid hormone (PTH) that are useful, for example, in the treatment or prevention of bone disorders such as osteoporosis. [A156, 159] The specific formulations recited in the claims are stable, liquid pharmaceutical formulations that comprise: (i) a high concentration of PTH (0.3-10 mg/ml); (ii) a buffer of pH 4 to 6; (iii) sodium chloride; (iv) mannitol; (v) a preservative; and (vi) water. [A1; A67]

Human PTH is a protein that is involved in calcium and phosphorous homeostasis and control of bone growth and density. [A2; A156] Forms of PTH that are useful in the claimed invention include full-length PTH (which comprises 84 amino acid residues) and fragments of PTH, such as PTH (1-34) (which comprises the first 34 N-terminal amino acid residues). [A159] Traditionally, PTH is given by intravenous or subcutaneous administration of a liquid formulation, see, e.g., Holthuis, col. 1, ln. 22-25 [A75], but the invention also includes alternative routes of administration [A159].

"Approximately 10 million American women have advanced osteoporosis and another 18 million women are . . . approaching osteoporosis, and are at high risk of fractures because of low bone density." [A297] "Osteoporosis is responsible for more than 1.5 million fractures annually," and "an average of 24 percent of hip fracture patients age 50 or over die within one year after their fracture." [A297]

Osteoporosis is similar to diabetes in that it is a chronic condition requiring repeated treatments. PTH treatment of osteoporosis often requires daily doses of PTH. [A122; A298; A301] Conventionally, PTH is provided as a lyophilized (freeze-dried) preparation that is reconstituted into a liquid solution prior to administration. Holthuis, col. 1-2 [A75].

At the time the invention was made, Applicants faced the problem of making a concentrated liquid formulation of PTH that would be stable and practical for use in the treatment of osteoporosis. [A156-157] Concentrated protein solutions were known to exhibit aggregation and precipitation, which are highly undesirable because they adversely affect both the available protein drug concentration and the physical and biopharmaceutical properties of the protein formulations. [A2; A157] Of direct relevance to the challenge faced by Applicants was prior art reporting that concentrated solutions of PTH formed aggregates. [A2; A157] One common way to reduce protein aggregation and precipitation is to reduce the concentration of protein. However, more dilute PTH formulations are not desirable because they require administration of a larger volume per dose, and increased dose volume makes the product more expensive to produce, requires larger delivery devices, and causes more discomfort upon administration. [A157] PTH also is known to be particularly sensitive to various forms of degradation which cause partial or complete loss of bioactivity. [A2; A157-58] Efforts to avoid these problems have included modifying the pH of PTH formulations to very high or low values, but extreme pH causes chemical degradation of PTH and discomfort upon administration. [A2; A157] Thus, the development of PTH formulations requires particular care. Holthuis, col. 2, ln. 1-8 [A75].

Recognizing the difficulty of preparing stable, liquid formulations of PTH, the prior art, such as Endo and Holthuis, has focused on creating stable, lyophilized PTH formulations. It is well-known that the presence of water facilitates degradation reactions, such as oxidation, and that liquid PTH formulations are more prone to oxidation than lyophilized formulations. Because nearly all water is removed during a lyophilization process, see, e.g., Holthuis, col. 4, ln. 63 – col. 5, ln. 1 [A76], lyophilized formulations of PTH typically do not suffer from the same problems as liquid formulations. Nonetheless, lyophilized formulations still must be prepared and stored with care. Holthuis, col. 2, ln. 1-8 [A75]; Endo, col. 1, ln. 14-27 [A80].

Through the present invention, Applicants have solved problems encountered in the prior art by providing stable, liquid PTH formulations that comprise high concentrations of PTH. [A1; A67] The formulations of the present invention can be used for multiple administrations. [A3; A159] For example, in a commercial embodiment of the invention, a stable, liquid PTH formulation is provided from which multiple doses can be self-administered over a period of 1 to 2 weeks. The ability to use a single liquid PTH formulation for multiple administrations over a period of 1 to 2 weeks (or longer) offers significant advantages of convenience and economy that benefit both health care providers and patients. [A159]

B. SUMMARY OF THE CITED REFERENCES

There are five main references discussed in the Board decision on appeal: (1) Holthuis, (2) Endo, (3) the '724 application, (4) MARTINDALE: THE EXTRA PHARMACOPEIA, The Pharmaceutical Press, London, 29th Edition, 1989 ("Martindale 1989"), and (5) MARTINDALE: THE EXTRA PHARMACOPEIA, The Pharmaceutical Press, London, 31st Edition, 1996 ("Martindale 1996"). A brief summary of the teachings of each is set forth below.

1. Holthuis

U.S. Patent No. 5,496,801 to Holthuis was filed December 23, 1993 and issued March 5, 1996. [A71] Holthuis is directed to lyophilized (freeze-dried) formulations of PTH stabilized with an excipient and a buffering agent. Holthuis, Abstract & col. 2, ln. 16-26 [A71, A75]. Holthuis discloses PTH formulations "in a powder form containing not more than 2% water by weight, that results from the freeze-drying of a sterile, aqueous hormone solution." Holthuis, col. 1, ln. 26-31 [A76]. The formulations of Holthuis comprise (a) PTH, (b) an excipient, such as a polyol, and (c) a buffering agent, such as citrate. Holthuis, Abstract & col. 7, ln. 40-48 [A71, A78]. There is no teaching or suggestion in Holthuis of including any amount of sodium chloride in its formulations.

Holthuis teaches that its lyophilized PTH formulations can be reconstituted in sterile water for parenteral injection. Holthuis, col. 2, ln. 33-37; col. 5, ln. 24-27

[A75, A77]. Although the "Background" section of Holthuis mentions that prior art PTH preparations were "prepared in water-based vehicles such as saline or water acidified . . . to solubilize the hormone," Holthuis, col. 1, ln. 34-37 [A75], there is no teaching or suggestion in Holthuis of reconstituting its lyophilized formulations, which may comprise relatively high amounts of PTH, with anything other than sterile water.

Holthuis indicates that reconstituted doses of its PTH formulation "can be refrigerated for subsequent use within a time frame of several days." Holthuis, col. 5, ln. 55-56 [A77]. However, Holthuis does not discuss or test the stability of its reconstituted formulation.

The background section of Holthuis includes a reference to Martindale 1989. Holthuis, col. 1, ln. 62-64 [A75]. Through that reference, Holthuis informs those skilled in the art of the conventional wisdom that sodium chloride should not be used in solutions of PTH. Martindale 1989, pg. 1338, col. 1 [A122].

2. Endo

U.S. Patent No. 5,563,122 to Endo issued October 8, 1996, from the U.S. national stage of a PCT application filed December 8, 1992 with a priority claim to two Japanese patent applications filed December 9, 1991 and November 24, 1992. [A79] Like Holthuis, Endo is directed to lyophilized preparations of PTH; Endo does not even consider the stability of liquid PTH preparations.

Endo was attempting to address the problem that "when mannitol is used as a stabilizing agent for lyophilized preparations of PTH used for injectable solutions, its stabilizing effect is unsatisfactory." Endo, col. 1, ln. 23-25 [A80]. The invention described in Endo is based on the "unexpected[] discover[y] that dramatically improved stability for lyophilized preparations of PTH can be obtained by combining a constant amount of sodium chloride with a sugar together before lyophilization." Endo, col. 1, ln. 30-34 [A80]. Notably, because Endo is not concerned with preparations of PTH in liquid form, Endo does not address the effects of sodium chloride on liquid PTH formulations.

Endo teaches that several different types of aqueous media can be used to prepare the PTH formulation to be lyophilized. Endo, col. 2, ln. 22-26 [A80]. Among the suitable aqueous media are "distilled water for injection" and "saline." Endo, col. 2, ln. 23-25 [A80]. That teaching, however, does not suggest that Endo's lyophilized preparation can be reconstituted with saline. Indeed, Endo does not provide any information on how to reconstitute its lyophilized PTH preparations. The only PTH solutions taught by Endo are the solutions from which the lyophilized preparations are made. Endo, col. 1, ln. 44-47; col. 2, ln. 32-34 [A80]. Even those solutions have much lower concentrations of PTH than the high concentrations recited in the instant claims, as seen in Endo's examples. [A80-81]

Endo studied the stability of its lyophilized preparations after they had been stored for three months at 40° C, using high performance liquid chromatography (HPLC). Endo, Example 2 & col. 5, ln. 18-49 [A80, 82]. Although the lyophilized preparations must have been dissolved in a liquid for HPLC analysis, Endo does not describe that process. [A80-82] Presumably, a standard HPLC solvent, such as acetonitrile, was used. Such a solution would not be suitable for pharmaceutical use.

Endo teaches that its lyophilized PTH preparations can be formulated into dosage forms comprising 1 μg – 150 μg PTH. Endo, col. 2, ln. 36-40 [A80]. Endo states that the dosage form will preferably be in the form of "an injectable lyophilized preparation." Endo, col. 2, ln. 36-40 [A80]. However, Endo provides no information or guidance on how to formulate its lyophilized preparation into an injectable form.

3. The '724 Application

Canadian Patent Application No. 2,234,724 was published April 24, 1997. [A84] The application was filed October 17, 1996, and claims priority to a German patent application filed October 17, 1995. [A84] The '724 application is directed to "pharmaceutical preparations which contain parathyroid hormone...in the form of lyophilisates or injection solutions." [A85] The '724 application teaches PTH solutions having high concentrations of PTH (e.g., up to 2, 5 or 10 mg/mL). [A87]

The '724 application expressly teaches away from the use of sodium chloride in PTH preparations.

The background section of the '724 application acknowledges that Endo disclosed stabilization of lyophilized PTH preparations by freeze-drying PTH preparations comprising sodium chloride.[1] [A85] The '724 application warns against Endo's approach, cautioning that "it has been shown that this type of stabilization favours the formation of dimers." [A85] The '724 application explains further that dimers are "problematic in pharmaceutical forms of administration since they can lead to undesired side-effects when administered to patients due to immunological reactions" and that "dimers can lead to a loss of activity." [A85-86] The '724 application contains data showing that dimers form in lyophilized PTH formulated with sodium chloride. [A94-95] Accordingly, the '724 application directs that "pharmaceutical forms of administration" of PTH "are preferably essentially free of chloride ions since chloride ions favour the formation of dimers." [A87-88]

[1] As discussed in more detail below, EP 0 619 119 cited in the '724 application is the European equivalent of U.S. Patent No. 5,563,122 ("Endo").

4. Martindale 1989

As noted in its Preface, Martindale 1989 provides "unbiased concise reports on the actions and uses of the world's drugs and medicines."[2] Martindale 1989 includes monographs on about 4000 substances, including PTH [A122].

The entry for PTH contains five different headings plus subheadings, including "Units," "Adverse Effects and Precautions," "Absorption and Fate," "Uses and Administration" and "Preparations." [A122] In the second paragraph of the PTH entry, Martindale 1989 informs that "[s]odium chloride solutions should not be used [with solutions of PTH] as they often cause precipitation." [A122]

5. Martindale 1996

Martindale 1996 is a later edition of Martindale 1989 that similarly contains a compendium of information on drugs and medicines. Martindale 1996 includes more monographs than Martindale 1989, with about 4458 monographs on drugs, as indicated in its Preface.[3]

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[2] The Preface of Martindale 1989 was not of record before the Board, but is included in the copy of Martindale 1989 in the Addendum to this Brief for the Court's convenience.

[3] The Preface of Martindale 1996 was not of record before the Board, but is included in the copy of Martindale 1996 in the Addendum to this Brief for the Court's convenience.

The entry for PTH in Martindale 1996 is much shorter and contains far less information than the entry in Martindale 1989. [A138] For example, where Martindale 1989 contained about nineteen paragraphs of information on PTH under five different headings, Martindale 1996 contains only three paragraphs on PTH. [A122; A138]

Information that is not included in Martindale 1996 includes information on the use of PTH to treat osteoporosis, the adverse effects of PTH overdose, the metabolism of PTH, the fact that PTH solutions can be diluted with glucose for injection, and the temperature at which PTH should be stored. [A122; A138] Martindale 1996 also does not contain the express warning against using sodium chloride in solutions of PTH that is set forth in Martindale 1989. [A122; A138] Martindale 1996 does not state or suggest that the warning was omitted because of a change in the state of the art, and certainly does not state or suggest that sodium chloride should be used in solutions of PTH. [A138]

C. THE BOARD DECISION ON APPEAL

The Board decision on appeal upheld the obviousness rejection of the present claims based on Holthuis and Endo. [A2] Holthuis was cited for teaching a PTH formulation comprising a high concentration of PTH, mannitol, and a buffer, that is prepared in liquid form and then lyophilized. [A3] The Board noted that Holthuis teaches that its lyophilized preparation can be reconstituted and

"refrigerated for subsequent use within a time frame of several days." (citing Holthuis, col. 5, ln. 55-56 [A77]) [A3]. The Board recognized that Holthuis does not teach or suggest the use of sodium chloride in its PTH formulation, but found that Endo provided such a teaching. [A3-4] Specifically, Endo is cited for teaching that the "addition of sodium chloride, in the presence of mannitol, further stabilizes PTH" and that "distilled water [or] physiological saline . . . can be used to reconstitute the lyophilized composition containing PTH."[4] (citing Endo, col. 1, ln. 29-34 & col. 2, ln. 22-24 [A80]) [A3-4]. The Board concluded that the combination of Holthuis and Endo rendered the invention obvious. [A5]

In response to Applicants' arguments that both Holthuis and Endo are directed to lyophilized preparations and do not teach or suggest the claimed stable, liquid PTH formulations, the Board stated that "each reference teaches reconstitution of the lyophilized preparation into a liquid preparation before administration." [A5] The Board also found that Holthuis' remark that its reconstituted formulation can be stored for use within a few days meets the "stable, liquid" recitation in the claims. [A6]

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[4] This is an erroneous reading of Endo. As explained below, the cited passages relate to the aqueous medium from which the lyophilized preparation is made, not to solutions used for reconstitution. Endo, col. 2, ln. 22-24, 50-59; col. 1, ln. 42-46 [A80]. Applicants find no teaching in Endo of suitable liquids for reconstitution, and no indication that sodium chloride would stabilize a liquid formulation of PTH.

The Board rejected Applicants' arguments of non-obviousness based on the teaching away from the claimed invention found in Martindale 1989. The Board apparently acknowledged that Martindale 1989 warns against using sodium chloride in PTH solutions because sodium chloride often causes precipitation, but disregarded that teaching as outdated. [A6-7] The Board found and newly cited an "updated" version of Martindale, Martindale 1996, and determined that Martindale 1996 was "more pertinent to the state of the art at the time of filing" (emphasis omitted). [A6; A11] Noting that Martindale 1996 "fails to include the warning on precipitation," the Board assumed that the use of sodium chloride in liquid PTH formulations was not contrary to the state of the art at the time the application was filed. [A6-7]

Applicants also had emphasized that the '724 application explicitly teaches away from the claimed invention. Specifically, Applicants highlighted the statements in the '724 application that sodium chloride should be avoided in PTH solutions because it "favours the formation of dimers" which are "problematic in pharmaceutical forms of administration." [A85-86] The Board disregarded the teachings away in the '724 application, alleging that Endo "was able to achieve the results [the '724 application] cautions against," [A7-8] even though Endo does not investigate dimer formation. The Board also asserted that Endo was more relevant to the claimed invention because Endo teaches the use of mannitol (as recited in

the instant claims) where the '724 application teaches the use of sucrose [A8], even though Endo teaches the use of sugars generally, including mannitol, sucrose and a number of other sugars [A80, 82-83]. Notwithstanding that the '724 application was filed and published after Endo, and explicitly addresses the approach taught by Endo, the Board concluded that Endo was "a better reflection of the state of the art" and outweighed the teachings away of the '724 application. [A7-8]

The Board therefore affirmed the rejection of claims 1-7, 9, 12, 17, 18, 20-28 and 31-36 as being obvious under §103.[5]

VI. SUMMARY OF THE ARGUMENT

The prior art of record fails to establish the obviousness of the rejected claims under § 103. "The ultimate determination of whether an invention is or is not obvious is a legal conclusion based on underlying factual inquiries including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the prior art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness." In re Dembiczak, 175 F.3d 994, 998

[5] Claims 20 and 25 were rejected over the combination of Holthuis, Endo, and an additional reference, U.S. Patent No. 5,547,939 ("Selsted"). [A1-2] Applicants did not separately argue the patentability of claims 20 and 25 before the Board. [A25] If the Court reverses the Board's obviousness rejection of claims 1-7, 9, 12, 17, 18, 21-24, 26-28 and 31-36, the Court also should reverse the obviousness rejection of claims 20 and 25, because both rejections cite Holthuis and Endo as the primary references.

(Fed. Cir. 1999). This Court reviews the Board's legal conclusion of obviousness de novo, and reviews its factual findings for substantial evidence. In re Gartside, 293 F.3d 1305, 1312 (Fed. Cir. 2000). Where the Board's factual findings are not supported by substantial evidence, this Court must reverse the Board's conclusions on obviousness. See, e.g., In re Zurko, 258 F.3d 1379, 1386 (Fed. Cir. 2001). In this case, a lack of substantial evidence infects several core factual findings supporting the Board's obviousness determination, including the findings on Applicants' teaching away arguments, the interpretation and application of Endo, and the finding of motivation to combine. Because the factual findings underlying the Board decision on obviousness are not supported by substantial evidence, the decision should be reversed.

The Board ignored a clear and unequivocal teaching away from the present invention that is set forth in Martindale 1989 because a later edition of Martindale (Martindale 1996) does not contain the same warning against the approach taken by the present invention. [A6-7] The Board assumed that the differences in the later edition reflected a change in the state of the art, but that assumption is not supported by any evidence of record, and is contradicted by other wholesale editorial changes made to Martindale 1996. [A122; A138] Because the Board's dismissal of Martindale 1989's teaching away is not supported by substantial evidence, the obviousness rejection that ignored that teaching away should be

reversed. See, e.g., In re Haruna, 249 F.3d 1327, 1336 (Fed. Cir. 2001) (reversing an obviousness rejection where the art taught away from the invention).

The Board erroneously interpreted Endo as being relevant to the claimed invention, even though Endo is directed to stabilizing PTH that is in lyophilized form while the invention is directed to stable PTH in liquid form. [A5] No evidence of record supports the Board's assumption that those skilled in the art would have considered Endo's teachings to be relevant to the present invention. Indeed, the teaching away in Martindale 1989, which primarily relates to liquid PTH formulations, shows that those skilled in the art recognized that liquid formulations are subject to different problems than lyophilized preparations. [A122] Additionally, the '724 application recognizes Endo's disclosure of the use of sodium chloride to stabilize lyophilized PTH preparations, but still advises that sodium chloride should be avoided in solutions of PTH (i.e., liquid PTH formulations). [A85-87]

The Board's assertion that Endo teaches reconstitution of its lyophilized PTH preparations is based on an erroneous reading of the reference. The passage of Endo cited by the Board relates to aqueous media from which the lyophilized preparation can be made, not to solutions for reconstitution. [A4] (citing [A41] (citing Endo, col. 2, 4th ¶ [A80])). Moreover, Endo does not teach or suggest that its PTH preparations, once reconstituted, would be stable, as required by the

present claims. The only stability data in Endo relate to the stability of its lyophilized formulations. [A80-82]

The Board's interpretation of Endo as contradicting the teachings away found in Martindale 1989 and the '724 application [A7-8] is not supported by substantial evidence because Endo does not address the problems that those references attribute to sodium chloride: precipitation of PTH and dimer formation. Martindale 1989 teaches that sodium chloride should not be used in solutions of PTH because it may cause the PTH to precipitate out of solution. [A122] Endo does not contain any teachings about the stability of its PTH preparations after reconstitution, does not examine any liquid PTH preparations for precipitated PTH, and does not indicate that its PTH preparations, once reconstituted, would be free of precipitate over any period of time. The '724 application warns against the use of sodium chloride in PTH preparations, as taught by Endo, because sodium chloride may promote the formation of dimers. [A85-86] Endo does not teach that its PTH preparations are free of dimers, does not examine its PTH preparations for dimers, and does not even consider the stability of liquid PTH preparations.

Because Endo does not address the stability of its PTH preparations once reconstituted, and does not even suggest that such reconstituted PTH preparations could be stored for any period of time without encountering the problems taught by Martindale 1989 and the '724 application, it simply cannot provide the specific

teachings required to rebut the teachings away set forth in those references, particularly where the '724 application directly criticizes the approach taken by Endo. See In re Lunsford, 357 F.2d 385, 389-390 (CCPA 1965).

The Board's findings of motivation to combine Holthuis and Endo also lack substantial evidence support. The Board accepted the Examiner's assertion that it would have been obvious to reconstitute the lyophilized PTH preparation of Holthuis with saline because saline is "one of the most commonly used pharmaceutically acceptable carriers" [A4] but there is absolutely no evidence of record to support that assertion. Indeed, the teachings in Martindale 1989 and the '724 application show that those skilled in the art would not have chosen to reconstitute a lyophilized PTH preparation with saline because saline (sodium chloride) was known to have detrimental effects on liquid PTH preparations.

The Board also accepted the Examiner's assertion that it would have been obvious from Endo to include sodium chloride in Holthuis' PTH preparation because Endo teaches that "sodium chloride . . . stabilizes PTH." [A4] That assertion is not supported by substantial evidence because it ignores the fact that Endo is directed to stabilizing lyophilized PTH preparations [A80], and in no way suggests that sodium chloride has a stabilizing effect on liquid PTH preparations, as claimed. The finding of motivation to combine is further undermined by the teachings away of Martindale 1989 and the '724 application, which show that

those skilled in the art would expect that including sodium chloride in a liquid PTH formulation would provide an unstable formulation that would not be suitable for pharmaceutical use, instead of the stable, liquid pharmaceutical formulations provided by the present invention.

A review of the evidence of record reveals no teaching or suggestion in the prior art that would lead someone skilled in the art to combine Holthuis and Endo to arrive at the claimed invention with any expectation of success in achieving a stable, liquid PTH formulation comprising sodium chloride. On this record, therefore, the Board decision should be reversed. See, e.g., In re Dow Chem. Co., 837 F.2d 469, 473 (Fed. Cir. 1988).

VII. ARGUMENT

A. STANDARD OF REVIEW

The ultimate issue on appeal, the obviousness of the claimed invention, presents an issue of law which the Court reviews without deference to the Board. Dembiczak, 175 F.3d at 998. "While this Court reviews the Board's determination in light of the entire record, an applicant may specifically challenge an obviousness rejection by showing that the Board reached an incorrect conclusion of obviousness or that the Board based its obviousness determination on incorrect factual predicates." In re Rouffet, 149 F.3d 1350, 1355 (Fed. Cir. 1998).

The factual findings underlying the Board's obviousness determination are reviewed for substantial evidence. In re Zurko, 258 F.3d 1379, 1384 (Fed. Cir. 2001). Applying this standard, the Court examines the record as a whole, considering evidence that both supports and detracts from the Board's conclusions. Id. Only if the Court finds evidence sufficient to allow a reasonable fact finder to reach the Board's conclusions can the Board's fact-finding be upheld. Gartside, 293 F.3d at 1312.

"A prima facie case of obviousness can be rebutted if the applicant can show that the art in any material respect taught away from the claimed invention." Haruna, 249 F.3d at 1335 (internal quotations omitted). "What a reference teaches and whether it teaches toward or away from the claimed invention are questions of fact." Winner Int'l Royalty Corp. v. Wang, 202 F.3d 1340, 1349 (Fed. Cir. 2000).

To establish a prima facie case of obviousness, there must be some showing of a teaching or motivation to combine the cited references. Dembiczak, 175 F.3d at 999. The requirement for motivation must be "rigorously" applied in order to guard again improper hindsight-based obviousness rejections. Id. "The presence or absence of a motivation to combine references . . . is a pure question of fact," reviewed under the substantial evidence standard. Gartside, 203 F.3d at 1305.

B. THE PRIOR ART OF RECORD FAILS TO ESTABLISH OBVIOUSNESS OF THE CLAIMED INVENTION

The invention recited in claims 1-7, 9, 12, 17, 18, 20-28, and 31-36 is not obvious in view of the cited prior art. To establish a prima facie case of obviousness the cited references must suggest the claimed invention as a whole, and the prior art must provide some motivation to combine the references in the manner asserted in the rejection. Gartside, 203 F.3d at 1319. Unless substantial evidence shows both a motivation to combine the references and a reasonable expectation of success, an obviousness rejection is improper and cannot be sustained. Dow, 837 F.2d at 473. Here, the primary references cited by the Board (Holthuis and Endo) do not suggest the present invention as whole. Moreover, the Board's findings on motivation to combine and expectation of success are not supported by substantial evidence. Under these circumstances, the Board decision should be reversed.

Both Holthuis and Endo are directed to lyophilized PTH preparations. Holthuis, col. 2, ln. 16-26; Endo, col. 1, ln. 29-34 [A75; A80]. In contrast, the present invention is directed to stable, liquid PTH formulations comprising a high concentration of PTH. [A1; A67] Other differences between the cited references and the invention include the absence from Holthuis of a suggestion to include sodium chloride in PTH preparations, and an absence from Endo of a suggestion of PTH formulations comprising high concentrations of PTH. Moreover, although

Endo teaches the use of sodium chloride to stabilize lyophilized PTH preparations, Endo does not teach or suggest liquid PTH formulations comprising sodium chloride, and does not teach or suggest that such liquid formulations would be stable, as required by the claims on appeal.

In determining the question of obviousness, one must consider "the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field." Dembiczak, 175 F.3d at 999. When the prior art teaches away from the claimed invention and shows that the invention is "contrary to the accepted wisdom" in the art, that is "strong evidence of non-obviousness." In re Hedges, 783 F.2d 1038, 1041 (Fed. Cir. 1986). The non-obviousness of the present invention is demonstrated by the understanding in the art at the time the application was filed that sodium chloride has detrimental effects on liquid PTH formulations. Both Martindale 1989 and the '724 application teach those skilled in the art to avoid using sodium chloride in liquid PTH formulations. [A122; A87-88] The Board's determination that the prior art does not teach away from the invention is not supported by substantial evidence, as shown below.

A finding of obviousness must be supported by a showing of "motivation to combine the references that create the case of obviousness." Rouffet, 149 F.3d at 1357. In the absence of reasons why someone skilled in the art "would select the elements from the cited prior art references for combination in the manner

claimed," the obviousness rejection must be reversed. Id. The prior art as a whole must both suggest the invention and provide a reasonable likelihood of success. Dow, 837 F.2d at 473. Here, where conventional wisdom in the art taught that liquid PTH formulations comprising sodium chloride are not stable, there can be no motivation to include sodium chloride in a stable, liquid PTH formulation as claimed. The Board's determination to the contrary lacks substantial evidence support.

For these reasons, the Board decision on obviousness should be reversed. See, e.g., Haruna, 249 F.3d at 1336 (reversing an obviousness rejection where the art taught away from the invention); Dow, 837 F.2d at 473 (reversing an obviousness rejection where "none [of the cited references] suggests that any process could be used successfully . . . to produce this product having the desired properties).

1. The Board's Disregard Of The Clear And Unequivocal Teaching Away In Martindale 1989 Lacks Substantial Evidence Support

The Board decision can and should be reversed based solely on its treatment of Martindale 1989. The Board's erroneous treatment of Martindale 1989 is not a factual one in any ordinary sense. Indeed, the error is apparent without knowing anything about the claimed technology or the substantive details of Martindale 1989. In essence, the issue is whether a teaching away that is found in an earlier

edition of a reference (Martindale 1989) necessarily is "erased" from the state of the art when that teaching is omitted without explanation from a later edition of the reference (Martindale 1996). A negative resolution of that issue requires reversal of the Board decision.

In reaching its obviousness determination, the Board disregarded a clear and unequivocal teaching away in Martindale 1989 because Martindale 1996, cited for the first time in the Board decision, does not contain the same teaching. [A6-7; A11] According to the Board, Martindale 1996 is "more pertinent to the state of the art at the time of filing" by virtue of its later publication date. [A6] In other words, the Board treated the omission of the teaching away from Martindale 1996 as erasing the teaching from the state of the art. The Board's decision to ignore the clear and unequivocal teaching away in Martindale 1989 because Martindale 1996 does not include the same information lacks substantial evidence support.

a. Martindale 1989 Specifically Warns Against The Use Of Sodium Chloride In Liquid PTH Formulations

"A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be lead in a direction divergent from the path that was taken by the applicant." In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994). Applying this standard, Martindale 1989 plainly teaches away from the claimed invention.

Martindale 1989 contains a clear and unequivocal warning to one of skill in the art to avoid the use of sodium chloride in liquid formulations of PTH. In the entry for PTH, the reference states: "Sodium chloride solutions should not be used as they often cause precipitation." Martindale 1989, pg. 1338, col. 1 [A122]. This admonition leads the skilled artisan in a direction divergent from the path that was taken by Applicants. Contrary to Martindale's warning that sodium chloride will cause PTH to precipitate, rendering liquid PTH formulations unstable and unsuitable for use, the present invention is able to provide stable, liquid PTH formulations that comprise sodium chloride.

b. Additional Prior Art Of Record Also Teaches Away From Sodium Chloride In Liquid PTH Formulations

The teaching away of Martindale 1989 is supported by another prior art reference of record, the '724 application. The '724 application teaches that mixtures of sodium chloride and PTH are undesirable because sodium chloride "favours the formation of dimers." [A86] The '724 application explains that dimers are "problematic in pharmaceutical forms of administration since they can lead to undesired side-effects when administered to patients due to immunological reactions" and "can lead to a loss of activity of the protein." [A85-86] The '724 application therefore advises that "pharmaceutical forms of administration" of PTH "are preferably essentially free of chloride ions since chloride ions favour the

formation of dimers." [A86] Like Martindale 1989, therefore, the '724 application teaches away from the claimed invention.

c. The Board Erroneously Treated The Martindale Revisions As Reflecting A Change In The State Of The Art

The Board's rationale for relying on Martindale 1996 instead of Martindale 1989 is that the 1996 edition was published closer to the filing date of the application and is "thus more pertinent to the state of the art at the time of filing" (emphasis omitted). [A6] The Board assumed that the absence in Martindale 1996 of the teaching away, admittedly found in Martindale 1989, reflected a change in the state of the art. [A6-7] No evidence of record supports that assumption.

Board decisions on obviousness must be supported by substantial evidence of record. Gartside, 203 F.3d at 1316. "[T]he Board cannot simply reach conclusions based on its own understanding . . . . Rather, the Board must point to some concrete evidence in the record in support of [its] findings." Zurko, 258 F.3d at 1386. Here, where no evidence supports the Board's assumption that the differences between Martindale 1996 and Martindale 1989 reflect a change in the state of the art, that finding, and the obviousness determination it supports, must be reversed. See id.

d. The Martindale Revisions Apparently Reflect Wholesale Editorial Changes To Martindale

The differences between the PTH entries for the two editions of Martindale appear to reflect wholesale editorial changes evident in the later edition that significantly shortened the PTH entry. Martindale 1996 contains far less information on PTH than Martindale 1989. Where the Martindale 1989 PTH entry contains 19 paragraphs of information, the Martindale 1996 entry contains only three paragraphs. [A122; A138] Martindale 1989 contains information on various aspects of PTH, including sections on "Units," "Adverse Effects and Precautions," "Absorption and Fate," and "Use and Administration." [A122] In contrast, Martindale 1996 contains none of these sections and omits nearly all of their information. [A138] Thus, it appears that wholesale editorial revisions were made between the 1989 and 1996 editions. It is likely that many revisions were necessitated by the larger number of entries contained in the later edition, which provides monographs on 4,458 substances, compared to the 4,000 substances listed in Martindale 1989.

The intermediate edition of Martindale, MARTINDALE: THE EXTRA PHARMACOPEIA, The Pharmaceutical Press, London, 30th Edition, 1993 ("Martindale 1993"), sheds further light on this issue.[6] The PTH entry in

[6] Martindale 1993 is included in the Addendum to this Brief.

Martindale 1993 is virtually identical to the entry in Martindale 1996. The preface of Martindale 1993 explains the changes from the previous edition (Martindale 1989), stating that the new edition was "markedly changed yet again in order to meet the requirements of today's readership." Specifically, Martindale 1993 was revised to "include a massive increase in information on proprietary medicines," and to reflect "a significant shift to a more clinical emphasis." The preface also notes that "[t]he monographs for all the drugs and substances . . . have been completely revised." The preface explains that "[t]he most obvious consequence of the changes that have been made for this edition is the increase in Martindale's size," with the 1993 edition being "467 pages bigger than its predecessor."

These wholesale editorial changes to Martindale do not support the Board's assumption that the differences between the PTH entries in Martindale 1989 and Martindale 1996 reflect a change in the state of the art. Because the teaching away in Martindale 1989 does not relate to proprietary medicines per se, and does not directly implicate clinical considerations, the differences between the PTH entries more likely reflect the shift in Martindale's focus noted in the preface of Martindale 1993.

Martindale 1993 was not of record during the proceedings before the Board. Applicants respectfully urge the Court to take judicial notice of the content of Martindale 1993 under FED. R. EVID. 201. Judicial notice is appropriate in this

instance because the content of Martindale 1993 (particularly the preface and PTH entry) is "not subject to reasonable dispute" and is "capable of accurate and ready determination by resort to sources whose accuracy cannot reasonable by questioned." See FED. R. EVID. 201(b); see also B.V.D. Licensing Corp. v. Body Action Design, Inc., 846 F.2d 727, 728 (Fed. Cir. 1988) (taking judicial notice that "the B.V.D. trademark is a least widely, if not universally, known"). Judicial notice also is appropriate because Martindale 1996 first was cited by the Board in the decision on appeal [A6-7, A11], and Applicants previously have not had an opportunity to address the Board's interpretation of that reference. Cf. Hines v. Sec'y Health & Hum. Servs., 940 F.2d 1518, 1526 (Fed. Cir. 1991) (noting that where a Special Master had taken judicial notice of a textbook, the appellant could have addressed the merits of the textbook during the review by the Claims Court).

With or without Martindale 1993, there is no evidence of record that the information omitted from Martindale 1996 was considered outdated or not valid at the time the 1996 edition was prepared. On the contrary, the evidence suggests that the omission was merely editorial. Moreover, other information omitted from Martindale 1996, such as the usefulness of PTH in the treatment of osteoporosis, clearly was not invalid or obsolete at the time. Thus, no substantial evidence supports the Board's assumption that the absence from Martindale 1996 of the

express teaching away found in Martindale 1989 reflected a change in the state of the art.

e. The Shorter PTH Entry In Martindale 1996 Does Not Erase The Teachings Of Martindale 1989

The Board disregarded the teaching away in Martindale 1989 because of "the lack of warning" in Martindale 1996. [A7] Yet, the absence of a teaching away in a later edition of a compendium such as Martindale does not erase the original teaching away, particularly where there is no evidence of a change in the state of the art.

"The Board must consider all of the applicant's evidence." Rouffet, 149 F.3d at 1355. Even references that are not cited as showing obviousness are "pertinent" if they "teach against the present invention." Dow, 837 F.2d at 473. "[T]he full field of the invention must be considered; for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention." Id. Without pointing to some prior art disclosure that liquid PTH formulations are unaffected by sodium chloride, the Board should not have disregarded Martindale 1989's teaching against the use of sodium chloride in liquid PTH formulations. See Lunsford, 357 F.2d at 389-390 (finding error where the Examiner ignored specific teachings without citing other references containing specific teachings demonstrating that the ignored teachings properly could be ignored).

Moreover, Endo in no way contradicts or "neutralizes" the teaching away of Martindale 1989. As discussed in more detail below, Endo relates to the use of sodium chloride to stabilize lyophilized (freeze-dried) PTH formulations. Endo, col. 1, ln. 29-34 [A80]. There is no suggestion in Endo that sodium chloride could stabilize liquid PTH formulations. Endo also lacks any teaching regarding the stability of liquid PTH formulations reconstituted from Endo's lyophilized PTH preparations.

The '724 application provides further evidence that the teaching away in Martindale 1989 remained pertinent and accurately reflected the state of the art at the time Applicant's patent application was filed. The application on appeal was filed April 26, 1999, and claims priority to a Swedish patent application filed April 28, 1998. The '724 application was published April 24, 1997, and claims priority to a German patent application filed in 1995. In contrast, Endo was filed years earlier, in 1992, and claims priority to a Japanese patent application filed December 9, 1991. The '724 application therefore more closely reflects the state of the art at the time of Applicant's invention. As discussed in more detail below, the '724 application expressly acknowledges the teachings of Endo, and teaches that Endo's approach "favours the formation of dimers," which are problematic in pharmaceutical preparations. [A84] Thus, the '724 application shows that Martindale 1989's warning against the use of sodium chloride in liquid solutions of

PTH remained valid at the time of Applicant's invention, notwithstanding the teachings of Endo. On the present record, therefore, the Board's decision to ignore the teaching away of Martindale 1989 represents a failure to consider all evidence bearing on the issue of obviousness, as required under §103.

When all prior art of record is evaluated as it would have been viewed by those skilled in the art at the time the application was filed, the non-obviousness of the claimed invention is apparent. Both Martindale 1989 and the '724 application warned those skilled in the art to avoid using sodium chloride in liquid PTH formulations. [A122; A87-88] The claimed invention, which provides a stable, liquid PTH formulation comprising sodium chloride, is contrary to that conventional wisdom, and therefore non-obvious. See, e.g., Winner, 202 F.3d at 1349-50 (noting that if a reference "did in fact teach away . . . that alone can defeat [an] obviousness claim); Hedges, 783 F.2d at 1041 (finding "strong evidence of unobviousness" where the invention was "contrary to the accepted wisdom").

2. The Board's Finding Of Obviousness Based On Endo Lacks Substantial Evidence Support

The Board's finding of obviousness relies on Endo for the teaching of a PTH formulation comprising sodium chloride. [A4] However, Endo does not teach or suggest the use of sodium chloride in stable, liquid PTH formulations, as recited in the claims on appeal. The Board's extension of Endo's teachings to liquid formulations of PTH is not supported by any evidence of record.

a. Endo Is Directed To Stabilizing Lyophilized PTH

Endo is directed to the use of sodium chloride to stabilize PTH that is in lyophilized form. Endo, col. 1, ln. 29-34 [A80]. There is no evidence of record that the skilled artisan would have considered Endo's teachings relating to the stabilization of lyophilized formulations to be relevant to liquid formulations. Indeed, the warning in Martindale 1989 that sodium chloride causes PTH to precipitate from solution shows that liquid PTH formulations are subject to different problems than lyophilized preparations. Additionally, the teaching in the '724 application against the use of sodium chloride in PTH solutions is made in direct contrast to Endo's teaching that sodium chloride may be used to stabilize lyophilized PTH formulations. [A85, 87-88] In this respect, this case is like In re Baker Hughes Inc., 215 F.3d 1297, 1303 (Fed. Cir. 2000), where the Court found that references related to gaseous hydrocarbons did not render obvious an invention directed to liquid hydrocarbons.

No substantial evidence supports the Board's extension of Endo's teaching that sodium chloride may stabilize lyophilized forms of PTH to arrive at the present invention, which relates to stable, liquid formulations of PTH. Thus, the Board's obviousness decision should be reversed. See Zurko, 258 F.3d at 1386 ("[T]he Board must point to some concrete evidence in the record in support of [factual findings].")

The Board attempts to dodge the differences between Endo and the claimed invention by noting that Endo contemplates the reconstitution of its lyophilized preparation into a liquid suitable for injection. [A5] However, the passage of Endo cited by the Board relates to aqueous media from which the lyophilized preparation can be made, not to solutions for reconstitution. [A4] (citing [A41] (citing Endo, col. 2, 4th ¶ [A80])). Thus, the Board decision is based on an erroneous reading of Endo, and should be reversed. See Zurko, 258 F.3d at 1386 (reversing a Board conclusion of obviousness that "was based on a misreading of the references").

Although Endo indicates that its lyophilized PTH preparations can be formulated into "injectable" dosage forms, it provides no guidance on how to do so. Endo, col. 2, ln. 36-40 [A80]. Thus, while Endo teaches that its lyophilized PTH preparations can be made into dosage forms comprising 1 μg – 150 μg PTH, it provides no information on the solution to use for reconstitution or the final volume of the reconstituted dosage form. Without that information, Endo simply cannot teach or suggest a liquid PTH formulation having the specific PTH concentrations recited in the instant claims.

Moreover, there is no hint or suggestion in Endo that its PTH preparations, once reconstituted, would be stable, as required by the present claims. The stability data in Endo relate to preparations stored in lyophilized form for three

months. [A80-82] There is no suggestion that, once reconstituted, Endo's preparations would be stable for any amount of time. Additionally, as discussed in more detail below, Endo does not address the specific problems that Martindale 1989 and the '724 application warn against, i.e., precipitation and dimerization.

The Board also cited Holthuis for teaching stable reconstituted PTH solutions [A6], but Holthuis does not teach or suggest the use of sodium chloride in its lyophilized formulation, and teaches only the use of "sterile water" for reconstitution, Holthuis, col. 2, ln. 33-37 [A75].

Because nothing in the prior art of record suggests a stable, liquid PTH formulation comprising sodium chloride, as presently claimed, the obviousness rejection should be reversed. See, e.g., Dembiczak, 175 F.3d at 1000 (reversing an obviousness rejection where the evidence of record did not suggest the invention as a whole); Rouffet, 149 F.3d at 1357 (same).

b. Endo Does Not Undermine The Teachings Away Of Martindale 1989 And The '724 Application

The Board cites Endo as contradicting the teachings away found in Martindale 1989 and the '724 application [A7-8], but that reading of Endo is not supported by substantial evidence because Endo does not address the problems that those references attribute to sodium chloride.

As noted above, Martindale 1989 teaches that sodium chloride should not be used in solutions of PTH because it may cause the PTH to precipitate out of

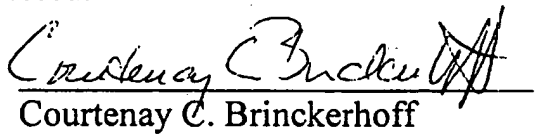
solution. [A122] Endo is directed to lyophilized preparations of PTH, not liquid solutions of PTH. Endo indicates that its lyophilized PTH preparations can be formulated into dosage forms that are "injectable," Endo, col. 2, ln. 36-40 [A80], but otherwise does not describe reconstitution of its lyophilized PTH preparations. Endo does not contain any teachings about the stability of its PTH preparations after reconstitution, does not examine any liquid PTH preparations for precipitated PTH, and does not indicate that its PTH preparations, once reconstituted, would be free of precipitate over any period of time. Thus, Endo does not contradict the teaching away of Martindale 1989.

The '724 application warns against the use of sodium chloride in PTH preparations because sodium chloride may promote the formation of dimers. [A85-86] Endo does not "contravene" that teaching, as alleged by the Board. Endo does not teach that its PTH preparations are free of dimers, does not examine its PTH preparations for dimers, and does not even consider the stability of liquid PTH preparations. Thus, no evidence supports the Board's assertion that "Endo was able to achieve the results the ['724 application] cautions against." [A7-8]

In addition, the warnings of the '724 application were provided with specific reference to the teachings of Endo. The '724 application cites EP 0 619 119 for disclosing stabilization of lyophilized PTH preparations by freeze-drying PTH preparations comprising sodium chloride. [A85] That EP document is the

VIII. CONCLUSION

The Board's determination that claims 1-7, 9, 12, 17, 18, 20-28 and 31-36 are obvious is erroneous as a matter of law. The Board's decisions to dismiss the teachings away of Martindale 1989 and the '724 application lack substantial evidence support. Moreover, the Board's determination that the teachings in Holthuis and Endo relating to lyophilized PTH formulations render obvious the claimed liquid PTH formulations is not supported by substantial evidence. Additionally, the Board's obviousness determination did not include a valid finding of motivation to combine the cited references, as required under §103. Thus, the Board decision affirming the rejection of claims 1-7, 9, 12, 17, 18, 20-26 and 31-36 under 35 U.S.C. § 103 should be reversed.



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European counterpart of Endo, as seen by a comparison of the inventors, priority documents, and disclosures of EP 0 619 119 and Endo.[7] [A79]. Thus, the Board's conclusion that "Endo is considered a better reflection of the state of the art" ignores the fact that the teaching away in the '724 application is made with express acknowledgement of the teachings of Endo.

The Board decision to give less weight to the '724 application than Endo also lacks substantial evidence support. The Board gave more weight to Endo because the '724 application discloses PTH formulations comprising sodium chloride and sucrose, while "Endo relates to the use of sodium chloride and mannitol," as recited in the present claims. [A7-8] There is no evidence of record that the use of a different sugar would make the teachings of the '724 application less relevant than the teachings of Endo. In fact, Endo is directed to the use of sodium chloride and sugars generally, and discloses and claims preparations where the sugar is sucrose, mannitol, or any one of a number of other sugars. Endo, col. 2, ln. 1-8 & Claims [A80, 82-83]. Moreover, the Board overlooked the fact that the '724 application was filed and published more contemporaneously to

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[7] EP 0 619 119 was not of record before the Board. However, Applicants respectfully urge the Court to take judicial notice of that document's correspondence to Endo, because that aspects of the document is not subject to reasonable dispute and is capable of accurate and ready determination. See FED. R. EVID. 201(b). EP 0 619 119 is included in the Addendum to this Brief.

Applicant's invention than Endo, and therefore more closely reflects the state of the art at the relevant time point. Thus, there is no support for the Board's decision to give more weight to Endo than to the '724 application.

Additionally, the weight given to Endo overlooks significant differences between Endo and the claimed invention discussed above, i.e., the fact that Endo is directed to preparations of PTH in lyophilized form, while the present invention relates to PTH formulations in liquid form. In emphasizing Endo, the Board improperly relied on "isolated teachings . . . without considering the over-all context within which those teachings are presented." In re Pagliaro, 657 F.2d 1219, 1225 (CCPA 1981). "Absent any reason to the contrary, it is [the closely related teachings of Martindale 1989 and the '724 application] which a person of ordinary skill in the art would consider most pertinent and accord the most weight." See Lunsford, 357 F.2d at 390. Because Endo does not address the stability of its PTH preparations once reconstituted, and does not even suggest that such reconstituted PTH preparations could be stored for any period of time without suffering from precipitation or dimerization, it simply cannot provide the specific teachings required to rebut the teachings away set forth in the other references of record. See id. "Because the factual findings underlying the Board's decision are not supported by substantial evidence," the obviousness determination should be reversed. Zurko, 258 F.3d at 1381.

3. The Board Did Not Make Out A Prima Facie Case Of Obviousness Because There Is No Motivation To Combine The Cited References To Arrive At The Invention

"To prevent the use of hindsight . . . to defeat patentability of the invention, this [C]ourt requires the examiner to show a motivation to combine the references that create the case of obviousness." Rouffet, 149 F.3d at 1357. "Although a reference need not expressly teach that the disclosure contained therein should be combined with another, the showing of combinality, in whatever form, must nevertheless by clear and particular." Winner, 202 F.3d at 1348-49 (internal quotations and citations omitted). Where, as here, motivation to combine is lacking, the invention is not obvious within the meaning of §103. See In re Kotzab, 217 F.3d 1365, 1371 (Fed. Cir. 2000).

The Board cited two assertions of the Examiner on the issue of motivation: (1) it would have been obvious to reconstitute the lyophilized PTH preparation of Holthuis with saline because saline is "one of the most commonly used pharmaceutically acceptable carriers;" and (2) it would have been obvious from Endo to include sodium chloride in the lyophilized PTH preparation of Holthuis which, upon reconstitution, would "yield a stable, liquid . . .composition comprising [PTH] and [sodium chloride]" as claimed. [A4] Neither assertion is supported by substantial evidence.

a. There Is No Motivation Evidenced in the Prior Art To Reconstitute Holthuis' Lyophilized PTH With Saline

The state of the art with regard to the reconstitution of lyophilized PTH preparations included the teaching in Martindale 1989 that sodium chloride should be avoided in PTH solutions [A122], the teaching in Holthuis that its preparation should be reconstituted with sterile water, Holthuis, col. 2, ln. 33-37 [A75], and the reference in Endo to "distilled water for injection," Endo, col. 2, ln. 22-23 [A80]. These teachings contradict the Examiner's unsupported assertion that saline would have been an "obvious" choice for reconstitution. Moreover, the Board cannot rely on "its own understanding or experience" when making "core factual findings in a determination of patentability," as it did here. See, e.g., Zurko, 258 F.3d at 1386.

The teachings of Martindale 1989 and the '724 application show that there would have been no expectation that a PTH preparation reconstituted with saline would be stable as recited in the present claims, because of their warnings about the precipitation and dimerization of PTH that is associated with sodium chloride in PTH solutions. The fact that Holthuis cites Martindale 1989 when discussing prior art PTH formulations, Holthuis, col. 1, ln. 62-64 [A75], shows that those skilled in the art reading Holthuis would have been informed of the conventional wisdom that sodium chloride has detrimental effects on PTH solutions.

Additionally, the only references that disclose high concentrations of PTH as claimed, Holthuis and the '724 application, specifically teach away from reconstitution with saline. Holthuis teaches reconstitution with sterile water, Holthuis, col. 2, ln. 33-37; col. 5, ln. 24-42 [A75, 77], and the '724 application warns against the use of sodium chloride in PTH solutions [A87-88]. Those skilled in the art would recognize that solutions with high concentrations of PTH are more prone to the problems Martindale 1989 and the '724 application warn against (precipitation and dimerization), and would follow the guidance provided in Holthuis and the '724 application. They would have no reason to turn to Endo, which does not address the stability of any type of PTH solution, let alone a solution with a high concentration of PTH. Accordingly, there is no evidence to support the assertion that one skilled in the art would have been motivated by Endo to reconstitute Holthuis' lyophilized PTH preparation with saline.

b. Endo Provides No Expectation Of Success In Achieving A Stable, Liquid PTH Formulation

Both the Examiner and the Board cite Endo for teaching that sodium chloride "stabilizes PTH" [A4], without acknowledging that Endo only addresses the stability of lyophilized PTH preparations, and not liquid PTH formulations as claimed.

Endo's focus on lyophilized preparations is plain. For example, Endo states that the invention provides "dramatically improved stability for lyophilized

preparations of PTH." [A80] The examples in Endo assess the stability of lyophilized preparations only, and the claims are directed to "[a] lyophilized preparation comprising [PTH.]" Endo, col. 5, ln. 61-65 [A82].

The teachings away of Martindale 1989 and the '724 application are further evidence of the lack of motivation to combine Holthuis and Endo in the manner asserted by the Board. As discussed above, both Martindale 1989 and the '724 application warn against the use of sodium chloride in PTH solutions. [A122; A85-88] The Board's disregard of these express teachings away was improper, for the reasons set forth above.

A review of the evidence of record reveals no teaching or suggestion in the prior art that would lead someone skilled in the art to combine Holthuis and Endo to arrive at the claimed invention with any expectation of success in achieving a stable, liquid PTH formulation comprising sodium chloride. Indeed, from Martindale 1989 and the '724 application, there would be an expectation of failure. On this record, therefore, the Board decision should be reversed. See, e.g., Dow, 837 F.2d at 473 (reversing an obviousness rejection where "none [of the cited references] suggests that any process could be used successfully . . . to produce this product having the desired properties").

In upholding the obviousness rejection of the present claims, the Board improperly used the claimed invention "as a blueprint for piecing together

elements in the prior art." See Rouffet, 149 F.3d at 1357. "[I]dentification of each claimed element in the prior art" is not "sufficient to negate patentability." Id. A "reference-by-reference, limitation by limitation analysis" with no motivation to combine fails to establish obviousness. Dembiczak, 175 F.3d at 1000. Thus, although the Board found prior art teaching isolated aspects of the invention, such as PTH formulations comprising sodium chloride and stable (lyophilized) PTH formulations, its determination that the invention is obvious does not satisfy the requirements of §103 because there is no teaching or suggestion of the invention as a whole, i.e., a stable, liquid PTH formulation that comprises sodium chloride. See 35 U.S.C. § 103. Accordingly, the obviousness rejection should be reversed.

ADDENDUM

1. Board Decision on Appeal
2. Claims on Appeal
3. Martindale 1989
4. Martindale 1993
5. Martindale 1996

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MARTIN BILLGER, and MIKAEL BRULLS

Appeal No. 2004-1216
Application No. 09/674,002

HEARD: JULY 13, 2004

Before WINTERS, ADAMS, and GREEN, Administrative Patent Judges.

GREEN, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-7, 9, 12, 17, 18, 20-28 and 31-36.[1] Claim 1 is representative of the subject matter of the appeal and reads as follows:

1. A stable, liquid pharmaceutical formulation of human parathyroid hormone at a concentration of 0.3 mg/ml to 10 mg/ml, comprising (i) human parathyroid hormone, (ii) a pharmaceutically acceptable buffer of pH 4 to 6 (iii) NaCl, (iv) mannitol, (v) a preservative, and (vi) water.

The examiner relies upon the following references:

Holthuis et al. (Holthuis)	5,496,801	Mar. 05, 1996
Selsted	5,547,939	Aug. 20, 1996
Endo et al. (Endo)	5,563,122	Oct. 08, 1996

[1] Claims 29 and 30 stand withdrawn from consideration, as being drawn to a non-elected invention.

Claims 1-7, 9, 12, 17, 18, 21-24, 26-28 and 31-36 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Holthuis and Endo et al. Claims 20 and 25 stand rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Holthuis and Endo as further combined with Selsted. After careful review of the record and consideration of the issues before us, we affirm both rejections.

BACKGROUND

"Human parathyroid hormone (PTH) is an 84 amino acid protein involved in calcium and phosphorus homeostasis and control of bone growth and density." Specification, page 1. "Human PTH may be obtained through tissue extraction, from peptide synthesis or from genetically engineered yeast, bacterial or mammalian cell hosts." Id. PTH may be used in the treatment of osteoporosis. See id.

The specification notes that increasing the concentration of many proteins increases their propensity to aggregate and precipitate, which is highly undesirable for the formulation of pharmaceutical preparations. See id. at 2. PTH, according to the specification, is a protein that is prone to aggregation when the concentration is increased. See id. Strategies that have been used to compensate for the aggregation include changing the pH of the solution, and increasing the dosage volume. See id. The specification also teaches that PTH is also particularly sensitive to various forms of degradation, and that the degradation reactions may lead to partial or complete loss of

PTH bioactivity. See id. at 2-3. The disclosed invention is thus drawn to a pharmaceutical formulation containing a relatively high concentration of PTH formulation in a liquid form that may be lyophilized and reconstituted prior to either single or multiple administrations. See id. at 4.

DISCUSSION

The examiner rejects claims 1-7, 9, 12, 17, 18, 21-24, 26-28 and 31-36 under 35 U.S.C. §103(a) as being obvious over Holthuis in view of Endo. See Examiner's Answer, page 3. As the claims stand or fall together, see Appeal Brief, page 2, we focus our analysis on the broadest claim, i.e., claim 1.

Holthuis is cited by the rejection for teaching "a pharmaceutical formulation comprising human parathyroid hormone (1-84), mannitol as an excipient, and citrate as buffering agent in both lyophilized and liquid form and a method for treating a bone related disorder, osteoporosis using the formulation." Examiner's Answer, page 3. Holthuis, according to the rejection, specifically teaches a PTH formulation comprising 0.09 mg/ml to 2.27 mg/ml human PTH, 50 mg/ml of mannitol, and 10mM citrate buffer at a pH between 4 and 6, wherein the formulation was prepared in liquid form and then lyophilized. See id. at 4. Holthuis further teaches the benefits of the use of a bacteriostatic agent during reconstitution, and teaches that the reconstituted protein may be refrigerated for subsequent use in the next several days. See id. The rejection acknowledges "Holthuis [ ] fail[s] to explicitly teach inclusion of sodium chloride (NaCl) in their pharmaceutical formulation." Id.

Endo is cited for teaching "that addition of sodium chloride, in the presence of mannitol, further stabilizes PTH," and for teaching "that distilled water, physiological saline (aqueous solution of NaCl) or buffer solutions can be used to reconstitute the lyophilized composition containing PTH." See id. at 4. The rejection concludes:

> Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to reconstitute the dried composition comprising PTH taught by Holthuis [ ] with saline, which would yield a stable, liquid pharmaceutical composition comprising NaCl, with a reasonable expectation of success. One would have been motivated to do so because saline is one of the most commonly used pharmaceutically acceptable carriers, as taught by Endo [ ] and Holthuis [ ].
>
> It would also have been obvious to one having ordinary skill in the art at the time the invention was made to include NaCl in the dried PTH formulation of Holthuis [ ], with a reasonable expectation of success. One would have been motivated to do so because Endo [ ] demonstrate[s] that addition of sodium chloride, in addition to mannitol further stabilizes PTH . . . . Reconstitution of the dried PTH formulation comprising NaCl with distilled water would yield a liquid pharmaceutical formulation comprising PTH and NaCl, which clearly reads on the instant claims.

Id. at 4-5.

"[T]he Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. '[The Examiner] can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references.'" In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (citation omitted). An adequate showing of motivation to combine requires "evidence that 'a skilled artisan, confronted with the same problems as the

inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.'" Ecolochem, Inc. v. Southern Calif. Edison Co., 227 F.3d 1361, 1375, 56 USPQ2d 1065, 1076 (Fed. Cir. 2000). We agree with the examiner that the combination of the references renders the composition of claim 1 obvious.

Appellants argue that the prior art does not teach a stable, liquid, human parathyroid hormone formulation. See Appeal Brief, page 5. Endo, according to appellants, added sodium chloride and mannitol to produce a stable lyophilized formulation. See id. Appellants contend that "there is no suggestion from Holthuis or Endo to generalize from a lyophilized to a liquefied parathyroid hormone formulation that can be stored for months at a time, and nothing in the prior art predicted or suggested Appellants' unexpected results." Id.

Claim 1 is drawn to "[a] stable, liquid pharmaceutical formulation of parathyroid hormone." As noted by the rejection, while both Holthuis and Endo pertain to lyophilized parathyroid hormone preparations, each reference teaches reconstitution of the lyophilized preparation into a liquid preparation before administration. Thus, the combination clearly teaches a liquid pharmaceutical formulation.

The issue thus narrows down to the use of "stable" in the claims. First, we note that during ex parte prosecution, claims are to be given their broadest reasonable interpretation consistent with the description of the invention in the specification. See In re Zletz, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1989). Nowhere in the

disclosure as filed, however, do the appellants tender a meaning for the term "stable." The specification discloses Tables examining the stability of different formulations, see Specification, pages 13-17, but the Tables all start at a time line of 0 days. See Specification, pages 13-17. We thus interpret "stable" to encompass the two to three days from reconstitution to administration as taught by Holthuis, and therefore find that the combination does teach a stable, liquid pharmaceutical formulation having the recited components.

Appellants argue further that the examiner failed to recognize the state of the prior art, in that it contravened conventional wisdom to incorporate sodium chloride into a highly concentrated parathyroid hormone formulation. See Appeal Brief, page 6. The appellants point out that Holthuis references "Martindale: The Extra Pharmacopoeia," which teaches away from incorporating PTH into a NaCl solution. See Id. at 7. According to appellants that reference teaches away from the claimed invention by teaching that "[s]oduim chloride solutions should not be used as they often cause precipitation." See Martindale: The Extra Pharmacopoeia, page 1338, The Pharmaceutical Press, London, 29th Ed., 1989. Appellant argues that Martindale is a general teaching relating reliable and unbiased information. See Reply Brief, page 2. The Martindale reference relied upon by appellants, however, was published in 1989, well before appellants' December 27, 2000 filing date. An updated version of the Martindale reference published in 1996, and thus more pertinent to the state of the art at the time of filing, fails to include the warning on precipitation. See Martindale: The

Extra Pharmacopoeia, page 742, Royal Pharmaceutical Society, London, 31st Ed., 1996. Thus we do not agree with appellants that the 1989 Martindale reference is sufficient evidence to rebut the prima facie case of obviousness given the lack of warning in the later Martindale, as well as the explicit teaching of Endo that addition of sodium chloride, in the presence of mannitol, further stabilizes parathyroid hormone formulations.

Appellants also cite CA 2,234,724 to support the assertion that the state of the art taught away from the use of sodium chloride in parathyroid hormone preparations. That reference, according to appellants, teaches that "sodium chloride 'favours the formation of dimers,' which are 'problematic in pharmaceutical forms of administration since they can lead to undesired side-effects when administered to patients due to immunological reactions.'" Appeal Brief, page 7. The reference is also cited by appellants for it's teaching that dimerization could lead to a loss of activity when stored over a long time. See id.

Again, we do not find that the teachings of the CA 2,234,724 reference as relied upon by appellants are sufficient to rebut the prima facie case of obviousness. Endo specifically encourages the use of sodium chloride, in combination with mannitol, as a method of stabilizing parathyroid formulations for long term storage, which contravenes the teachings of the CA 2,234,724 reference, relied upon by appellants. "When prior art contains apparently conflicting references, the Board must weigh each reference for its power to suggest solutions to an artisan of ordinary skill." In re Young, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (1991). Because Endo was able to achieve the

results the CA 2,234,724 reference cautions against, and as Endo relates to the use of sodium chloride and mannitol, as required by claim 1, whereas the CA 2,234,724 reference in Table I looks at the combination of sodium chloride and sucrose, Endo is considered a better reflection of the current state of the art.

With respect to the rejection of claims 20 and 25 over the combination of Holthuis and Endo as further combined with Selsted, Appellants argue that the antimicrobial agent in Selsted is a tryptophan –rich indolicidin protein analog, and not EDTA alone. See Reply Brief, page 4. Thus, appellants contend that "[a]t the very most, the skilled artisan would likely have been motivated to add indolicidin and EDTA to Holthuis' or Endo's PTH formulation, but would not have been motivated to add EDTA alone. Id. (emphasis in original). That argument is not convincing, however, as the use of the term "comprising" in the claims leaves the claims open to the addition of additional components, such as indolicidin, and the rejection is affirmed.

CONCLUSION

For the reasons stated above, the rejection of claims 1-7, 9, 12, 17, 18, 20-28, and 31-36 under 35 U.S.C. §103(a) is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

Sherman D. Winters)
Administrative Patent Judge)
)
)
Donald E. Adams) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
)
Lora M. Green) INTERFERENCES
Administrative Patent Judge)

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Notice of References Cited	Application/Control No. 09/674,002	Applicant(s)/Patent Under Reexamination Appeal No. 2004-1216	
	Examiner BPAI	Art Unit	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
X	U	"Martindale: The Extra Pharmacopoeia," Royal Pharmaceutical Society, 31st Edition, p. 742, (1996)
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

CLAIMS ON APPEAL

1. (Previously amended) A stable, liquid pharmaceutical formulation of human parathyroid hormone at a concentration of 0.3 mg/ml to 10 mg/ml, comprising (i) human parathyroid hormone, (ii) a pharmaceutically acceptable buffer of pH 4 to 6, (iii) NaCl, (iv) mannitol, (v) a preservative, and (vi) water.

2. (Previously amended) The pharmaceutical formulation according to claim 1, wherein the human parathyroid hormone is human recombinant parathyroid hormone.

3. (Previously amended) The pharmaceutical formulation according to claim 1, wherein the human parathyroid hormone is a full-length parathyroid hormone.

4. (Previously amended) The pharmaceutical formulation according to claim 1, wherein the concentration of the human parathyroid hormone is from 0.3 mg/ml to 5 mg/ml.

5. (Previously amended) The pharmaceutical formulation according to claim 4, wherein the concentration of the human parathyroid hormone is from 1 mg/ml to 3 mg/ml.

6. (Previously presented) The pharmaceutical formulation according to claim 1, wherein the pharmaceutically acceptable buffer is a citrate buffer at a concentration from 5 to 20 mM.

7. (Previously presented) The pharmaceutical formulation according to claim 1, wherein the pharmaceutically acceptable buffer has a pH between 5 and 6.

9. (Previously presented) A stable, liquid pharmaceutical formulation of human parathyroid hormone, comprising 1 to 3 mg/ml parathyroid hormone, 2 to 5 mg/ml

NaCl, 20 to 50 mg/ml mannitol, a preservative, and 5 to 10 mM citrate buffer at a pH between 4 and 6.

12. (Previously presented) A process for the preparation of a pharmaceutical formulation according to claim 1, comprising dissolving human parathyroid hormone, to a concentration from 0.3 to 10 mg/ml, sodium chloride, and mannitol in a pharmaceutically acceptable buffer having a pH between 4 and 6.

17. (Previously presented) A method for treating a bone related disorder or reducing or inhibiting bone loss associated with a bone related disorder, comprising administering to a mammal, including man, in need of such treatment or inhibition, an effective amount of the formulation of claim 1.

18. (Previously presented) The method according to claim 17, wherein the bone related disorder is osteoporosis.

20. (Previously added) The pharmaceutical formulation of claim 9, wherein the preservative is benzyl alcohol, m-cresol or EDTA.

21. (Previously added) The pharmaceutical formulation of claim 9, wherein the parathyroid hormone is human recombinant parathyroid hormone.

22. (Previously added) The pharmaceutical formulation of claim 9, wherein the parathyroid hormone is human full-length parathyroid hormone.

23. (Previously added) The pharmaceutical formulation of claim 9, wherein the pH of the citrate buffer is between 5 and 6.

24. (Previously presented) A stable, liquid pharmaceutical formulation comprising 1 to 3 mg/ml parathyroid hormone, 2 to 5 mg/ml NaCl, 20 to 50 mg/ml mannitol, 5 to 10 mM citrate buffer at a pH between 4 and 6, and a preservative.

25. (Previously added) The pharmaceutical formulation of claim 24, wherein the preservative is benzyl alcohol, m-cresol or EDTA.

26. (Previously added) The pharmaceutical formulation of claim 24, wherein the parathyroid hormone is human recombinant parathyroid hormone.

27. (Previously added) The pharmaceutical formulation of claim 24, wherein the parathyroid hormone is human full-length parathyroid hormone.

28. (Previously added) The pharmaceutical formulation of claim 24, wherein the pH of the citrate buffer is between 5 and 6.

31. (Previously added) The pharmaceutical formulation of claim 1, wherein the concentration of the NaCl is between 2 to 5 mg/ml.

32. (Previously added) The pharmaceutical formulation of claim 1, wherein the parathyroid hormone is human recombinant parathyroid hormone (1-84).

33. (Previously added) The pharmaceutical formulation of claim 9, wherein the parathyroid hormone is human recombinant parathyroid hormone (1-84).

34. (Previously added) The pharmaceutical formulation of claim 24, wherein the parathyroid hormone is human recombinant parathyroid hormone (1-84).

35. (Previously added) A method for treating a bone related disorder or reducing or inhibiting bone loss associated with a bone related disorder, comprising administering to a mammal, including man, in need of such treatment or inhibition, an effective amount of the formulation of claim 9.

36. (Previously added) The method according to claim 35, wherein the bone related disorder is osteoporosis.

Martindale, William

MARTINDALE

The Extra Pharmacopoeia

Twenty-ninth Edition

Edited by James E. F. Reynolds

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Assistant Editors
Anne V. Parsons
Sean C. Sweetman

Published by direction of the Council of the Royal Pharmaceutical Society of Great Britain and prepared in the Society's Department of Pharmaceutical Sciences

London
THE PHARMACEUTICAL PRESS
1989

 Published by The Pharmaceutical Press, 1 Lambeth High Street, London SE1 7JN, England.

The first edition of the Extra Pharmacopoeia was published in July 1883. Squire's Companion was incorporated in the twenty-third edition in 1952. The twenty-eighth edition was published in December 1982. This current (twenty-ninth) edition was published in January 1989.

BRITISH LIBRARY CATALOGUING-IN-PUBLICATION DATA

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Preface

This edition of Martindale continues the tradition of its predecessors in aiming to provide unbiased concise reports on the actions and uses of most of the world's drugs and medicines to aid the practising pharmacist and physician. While the overall format of this edition remains similar to that of the 28th edition, its contents are the result of a complete revision and the changes resulting from that revision have been considerable.

Monographs have been reorganised into chapters that more accurately reflect current therapeutic practice and the needs of today's reader. The 105 chapters of the last edition have been reorganised into 72 mainly new or renamed chapters. Details have been provided on about 900 new compounds, mostly in the form of new monographs. Over 500 monographs have been deleted where they described substances for which there is little evidence of continued use or interest. Almost 500 other monographs have been deleted where the information could be better incorporated in monographs for related compounds; information on the substances that were the subjects of these deleted monographs can still be traced through the index. The overall effect has been an increase in the coverage of drugs in Martindale, but with a considerable saving of space that has allowed us to make some typographical improvements to assist the reader in locating sections of a monograph.

Abstracts of the relevant aspects of important or useful papers and other publications are still included, but we have written many more referenced reviews of important or contentious topics to back up our editorial text. We have also continued to increase the coverage of proprietary names. More manufacturers are identified for the proprietary names that are included, the directory of manufacturers having increased by 50%. We have also started to include the proprietary names for preparations containing more than one active ingredient and our coverage now extends to many of the English speaking countries.

Considerable changes have been made to Martindale the better to reflect developments in therapeutics in the last 5 or 6 years. Some of the developments have been successful, some have still to produce worthwhile results or remain to be evaluated. A distressing and dominant theme throughout much of the period of revision has been the continuing search for an effective treatment of AIDS. The much enlarged chapter on antiviral agents illustrates some of this work, but it also shows the improvements that there have been in the treatment of other viral diseases. A more optimistic theme has been the expected and growing yield of products from genetic engineering techniques.

A considerable proportion of Martindale is taken up with drugs used to treat infections. Notable features, in addition to developments in antiviral therapy, include the emergence of the fluorinated quinolones and imipenem in the treatment of bacterial infections; the establishment of praziquantel in the treatment of schistosomiasis and other fluke infections; the consolidation of metronidazole and the re-emergence of pentamidine in protozoal infections; and the emergence of the anthelmintic ivermectin for the treatment of onchocerciasis, commendably provided free of charge through a WHO scheme. The increase in cephalosporins seems to continue inexorably.

Advances in the cardiovascular group of drugs have been wide ranging and encouraging. This edition shows the greater benefit that can now be obtained with thrombolytic, anticoagulant, antiplatelet, and haemostatic therapy. ACE inhibitors have established themselves in the treatment of hypertension. Calcium channel blockers continue to appear and offer a range of cardiovascular activity. Improvements have also taken place in lipid regulation.

Developments have continued in the field of peptic ulcer therapy. There are more histamine H2 antagonists, but there is also increased interest in tripotassium dicitratobismuthate in the light of the involvement of *Campylobacter pylori*. Work still progresses on the use of prostaglandins in peptic ulcer and there are new approaches to treatment as with the proton pump inhibitor, omeprazole.

There are other areas where advances are less dramatic, as for instance with antineoplastic agents or antiparkinsonian drugs. Resistance is a continuing concern with antimalarial compounds. Some chapters indicate a decrease in the use of drugs such as the anxiolytic sedatives and hypnotics. A number of nonsteroidal anti-inflammatory drugs have been withdrawn, but our files show that many more are being considered at development stages. Some general anaesthetics have been withdrawn because of toxicity associated with the solvent or vehicle, emphasising the often unregarded importance of formulation to therapeutics.

Martindale is based on published information. It is not a book of standards. Inclusion of a substance or a preparation is not to be considered as a recommendation for use, nor does it confer any status on the substance or preparation. While considerable efforts have been made to check the material in Martindale, the publisher cannot accept any responsibility for errors and omissions. Also the reader is assumed to possess the necessary knowledge to interpret the information that Martindale provides.

Arrangement

PART 1 (pages 1–1535) contains monographs on about 4000 substances arranged in 72 chapters. These chapters generally bring together drugs that have similar uses or actions. Cross-references are used to guide the reader to drugs that may be of interest in related chapters. Most chapters now have an introduction which provides background information on that group of drugs. Some drugs such as the corticosteroids can be considered readily as a group with its members having many common actions; in such cases the introduction provides much of the information for that chapter.

PART 2 (pages 1537–1631) consists of a series of short monographs on some 800 drugs and ancillary substances arranged in the alphabetical order of their main titles. It includes monographs on new drugs, on drugs under investigation, on drugs not easily classified, and on obsolescent drugs still of interest. There are also some monographs on toxic substances, the effects of which may require drug therapy.

PART 3 (pages 1633–43) gives the composition of some 670 proprietary medicines that are advertised to the public in Great Britain and that are usually supplied on demand. The formulas are generally as described by the manufacturers. Herbal medicines have been omitted. This list should not be considered to be comprehensive; some such proprietary medicines are included in Parts 1 and 2, usually if the preparation contains one active ingredient or if proprietary names for similar preparations from other countries are already listed under the monographs. As

in earlier editions of Martindale, the claims made for these products and their recommended doses are not included.

The number of 'counter' proprietary medicines continues to decline.

Indexes

DIRECTORY OF MANUFACTURERS. Throughout the text the names of manufacturers and distributors are abbreviated. Their full names are given in this directory together with the full address if it is available. This directory has considerably increased from about 3000 entries to 4600.

INDEX TO CLINICAL USES. This index is a guide to the uses described in the text; it should not be used otherwise and is not a comprehensive therapeutic index. It refers the reader to the chapters and monographs where the listed diseases are mentioned. The drugs under each disease heading are listed in alphabetical order and not in order of preference.

INDEX TO MARTINDALE IDENTITY NUMBERS. Each monograph in Martindale has an identity number which is used in our computer manipulation. These identity numbers are referred to in the databank (Martindale Online) and will mainly be of value to the user of the online service; however, they may also be of some value to the user of the book. The numbers have no structure and are not significant in themselves. The index lists the identity number followed by the relevant monograph title and the page on which it appears. Identity numbers for chapter introductions have also been included.

GENERAL INDEX. To make fullest use of the contents of Martindale the general index should always be consulted. The exhaustive index to the drugs, preparations, compounds, and pharmacological and therapeutic groups in the book has been compiled to exacting standards and this has resulted in an index of about 62 000 entries. As in previous editions, the index is arranged alphabetically 'word-by-word' rather than 'letter-by-letter'.

Nomenclature

MARTINDALE IDENTITY NUMBERS. Each monograph begins with an identity number which consists of a maximum of 6 figures followed by a check character. These numbers are used in our computer manipulation and their sole purpose is to identify monographs in Martindale. They are referred to in the databank and will mainly be of value to the user of the online or compact disc services; however, they may also be of value to the reader of the book.

TITLES AND SYNONYMS. The title of each monograph is in English, with preference being given to British Approved Names, United States Adopted Names, and International Nonproprietary Names. These 3 authorities are now shown where appropriate against our titles or synonyms. Names given as synonyms include commonly used abbreviated names; English, American, and Latin synonyms; names used in other languages when these may not be readily identifiable; manufacturers' code numbers; and chemical names. In some approved names it is now general policy to use 'f' for 'ph' in sulpha, 't' for 'th', and 'i' for 'y'; for this reason entries in alphabetical lists and indexes should be sought in alternative spellings if the expected spellings are not found. A table of contracted names for ions and groups used in approved names and titles is given on page xx.

CAS REGISTRY NUMBERS. Chemical Abstracts Service (CAS) registry numbers are provided, where available, for each monograph substance to help readers refer to other information systems. Numbers for various forms of the monograph substance are listed with the variation in form given in parenthesis.

Pharmacopoeias

The pharmacopoeias in which each substance appears are listed. Current copies of the pharmacopoeias and their addenda should be consulted for confirmation and for details of standards.

The pharmacopoeias covered include: Argentine, *Austrian*, *Belgian*, Brazilian, *British*, *British Veterinary*, *Chinese*, *Czechoslovakian*, *Egyptian*, *European*, *French*, *German*, Hungarian, *Indian*, *International*, *Italian*, *Japanese*, *Jugoslavian*, Mexican, *Netherlands*, Nordic, Polish, Portuguese, Roumanian, Russian, Spanish, *Swiss*, Turkish, and *United States* (including the *Formulary*). Those *italicised* in the above list either appeared as new editions or were revised by supplements since the last edition of Martindale, and have been examined for this 29th edition.

The abbreviations for these pharmacopoeias are included in the list of abbreviations used in Martindale, see page xvi which also includes details of the edition and/or supplement(s) consulted.

Atomic and Molecular Weights

Atomic weights are based on the table of Atomic Weights as revised in 1983 by the Commission on Atomic Weights and Isotopic Abundance, International Union of Pure and Applied Chemistry and based on the ^{12}C scale (see page xxx). Molecular weights are given corrected to one place of decimals or to four significant figures for relative weights of less than 100.

Pharmaceutical Information

Information on the chemical and physical properties of each substance is given where available and where it is likely to be of use or interest. Compared with earlier editions, this information has been much reduced and included only when it is certain that it applies to the form of substance being described in the monograph. Discrepancies in properties as described in the *B.P.* and *U.S.P.* are indicated.

PERCENTAGE STRENGTHS. Unless otherwise stated, solutions of solids in liquids are expressed as percentage w/v, of liquids in liquids as percentage v/v, and of gases in liquids as percentage w/w.

SOLUBILITY. The figures given for solubility in each monograph have generally been obtained from the major pharmacopoeias in which the substance is described, but should not be considered absolute. Unless otherwise indicated in the text, the figures are for solubility at 'ordinary room temperature' which is considered to be about 20°. Where solubilities are given in words, the following terms describe the indicated solubility ranges:

solubility	
very soluble	1 in less than 1
freely soluble	1 in 1 to 1 in 10
soluble	1 in 10 to 1 in 30
sparingly soluble	1 in 30 to 1 in 100
slightly soluble	1 in 100 to 1 in 1000
very slightly soluble	1 in 1000 to 1 in 10 000
practically insoluble	1 in more than 10 000

STORAGE. Substances and preparations should be stored under conditions which prevent contamination and diminish deterioration,

and the conditions of storage given in the text indicate the precautions recommended in specific cases. Where authorities differ, we have included the most stringent storage requirement. The term 'a cool place' is generally used to describe a place in which the temperature does not exceed 15°. Unless otherwise specified, all injections should be stored in alkali-free containers.

TEMPERATURE. Temperatures are expressed in degrees Celsius (centigrade) unless otherwise indicated.

Pharmacological and Therapeutic Information

Information on the adverse effects, treatment of adverse effects, precautions, absorption and fate, and uses and administration of each substance is provided by concise statements and these are elaborated and expanded by referenced reviews and abstracts from papers and other publications.

This edition contains about 35 500 abstracts or reviews based on information in an ever widening range of publications. In making our selection, we have tried to include the key papers. Where there has been a large body of work, abstracts of some typical papers have been provided with perhaps a selection of references. However, room has also been made for the interesting letter or case report where it is felt that information on a rare effect or action may be useful to the reader.

Much information has been found in sources such as World Health Organization publications, government reports and legislation, and other official and standard publications. Manufacturers' literature has been considered in the light of other available information.

The risks of administering drugs in pregnancy are well known and the general principle is to give a drug only when the benefit to the individual mother outweighs the risk to the foetus. Where there is a clear risk it is noted under the Precautions or Adverse Effects heading but safety should not be inferred from the absence of a statement for any drug.

Interactions are described under the Precautions heading with detailed information being provided in the monograph for the drug that is being affected.

Doses

Doses are described under the Uses and Administration heading with as much detail as is necessary and available. Unless otherwise stated the doses represent the average range of quantities which are generally regarded as suitable for adults when administered by mouth. More information on doses and drug administration may be given in the abstracts and under the Preparations sections. Unless otherwise specified, glucose injection is 5% w/v, sodium chloride injection is 0.9% w/v, and water is purified water.

When doses for children are expressed as a range of quantities within specified age limits, the lower dose applies at the lower age and the higher dose at the higher age.

Formulas

Official preparations are included from current editions of the *British Pharmacopoeia* and the *United States Pharmacopoeia* and *National Formulary*. Preparations from the *British Pharmaceutical Codex 1973* are included if still relevant and not covered by the *British Pharmacopoeia*. Preparations have also been included from the *Australian Pharmaceutical Formulary and Handbook*. The synonyms sometimes included for these preparations may be official synonyms or synonyms that are or have been in common use.

Proprietary Preparations

In Parts 1 and 2, the information on proprietary preparations available in the *UK* is presented with each product being described in the proprietary preparations section of the monograph on its principal ingredient.

Lists of the proprietary names of single-ingredient preparations have been provided for a range of countries including the *UK*. Proprietary names of multi-ingredient preparations have also been included for some countries under the monograph for each of the significant active ingredients. Minor ingredients have not been included.

Readers should be aware that these lists are provided for the purposes of identification. They thus include the names of discontinued preparations as well as names for products registered but still to be marketed.

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The Editor gratefully acknowledges the advice and assistance of the many experts who have suggested amendments to the text of Martindale. Special thanks are due to Heather M. Elliston, Margaret J. Gilmour, and P. Rowe for reading and commenting on drafts of this edition.

The Editor is grateful to the many organisations that have helped in providing information, including the British Pharmacopoeia Commission, the Medicines Division of the *UK* Department of Health, and the World Health Organization.

Martindale staff have been able to call freely on the expertise of other members of the Royal Pharmaceutical Society's staff. In particular the Editor is grateful to A. Wade, the General Editor, Anne B. Prasad and the editorial staff of the British National Formulary, and Pamela M. North and the staff of the library and information department.

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The contents of this 29th Edition were planned, written, checked, indexed, keyed, and proofed by the Martindale staff. It could not have been produced without that staff's commitment. The Editor welcomes this opportunity to record his gratitude and appreciation of the dedicated services of the clerical staff, Jacqueline O. Baines and Doris D. Moore, and of the editorial staff: Eileen J. Atchison, P. S. Blake, A. G. Deason, Kathleen Eager, Wendy M. Farenden, Anne M. P. Gilchrist, Ann Harris, Susan L. Jefferson, Julie M. McGlashan, Rosalind McLarney, and J. Martin. Finally, the Editor is indebted to the Assistant Editors, Anne V. Parsons and S. C. Sweetman, and especially the Deputy Editor, Kathleen Parfitt, for invaluable assistance and support.

London
October 1988

Martindale The Extra Pharmacopoeia,
The Pharmaceutical Press, London. 29th ed. 1989

Parathyroid Calcitonin and Biphosphonates

8050-t

The agents covered in this section are the calcium-regulating hormones, parathyroid hormone and calcitonin, and the biphosphonates. Parathyroid hormone and calcitonin are both involved in the regulation of plasma-calcium concentration, parathyroid hormone having a hypercalcaemic, and calcitonin a hypocalcaemic effect. Calcitonin is used in the treatment of hypercalcaemia, but parathyroid hormone is no longer used in the treatment of hypocalcaemia; agents used for hypocalcaemia include calcium salts (p.1028) and vitamin D substances (p.1282).

Calcitonin and the biphosphonates inhibit bone resorption and are used in the treatment of conditions associated with increased bone resorption and re-formation, such as Paget's disease of bone (osteitis deformans). The biphosphonates have been tried in the treatment of hypercalcaemia. Other agents used in the treatment of hypercalcaemia include corticosteroids (p.878), phosphate salts (p.1035), sodium sulphate (p.1107), and sodium cellulose phosphate (p.353). See also sodium fluoride (p.1616). Plicamycin (p.647) is used as an inhibitor of bone resorption.

A review of the hormonal regulation of plasma-calcium concentrations.— I. Macintyre, *Br. med. Bull.*, 1986, *42*, 343.

Studies and discussions on the possible role of calcium-regulating hormones in the regulation of blood pressure.— A. K. Sangal and D. G. Beevers, *Br. med. J.*, 1983, *286*, 498; A. Goulding (letter), *ibid.*, 1053; T. Christensson, *ibid.*, 1199; D. E. Grobbee and A. Hofman, *Lancet*, 1986, *2*, 703; G. M. A. Palmieri *et al.*, *ibid.*, 1106; L. M. Resnick *et al.*, *Ann. intern. Med.*, 1986, *105*, 649.

A review of the design, biological evaluation, and potential uses of parathyroid hormone antagonists.— M. Rosenblatt, *New Engl. J. Med.*, 1986, *315*, 1004.

8051-x

Parathyroid Hormone

Parathyrin; PTH.

CAS — 9002-64-6.

Parathyroid hormone is a single-chain polypeptide isolated from the parathyroid glands. It contains 84 amino acids and in man the first 34 appear to be responsible for the hormonal activity. The amino-acid sequence varies according to the source.

Solutions of parathyroid hormone for injection may be diluted with glucose 2.5 to 5%. Sodium chloride solutions should not be used as they often cause precipitation. They should be stored at a temperature not greater than 8°.

Units

200 units of parathyroid hormone, bovine, for bioassay are contained in approximately 0.6 mg of freeze-dried trichloroacetic acid extract of bovine parathyroid glands, with lactose 5 mg in one ampoule of the first International Reference Preparation (1976).

2 units of parathyroid hormone, bovine, for immunoassay are contained in approximately 1 µg of freeze-dried purified isohormone 1 from bovine parathyroid, with human albumin 200 µg and lactose 1 mg in one ampoule of the first International Reference Preparation (1974).

0.1 units of human parathyroid hormone for immunoassay are contained in 100 ng of freeze-dried purified hormone with human serum albumin 250 µg and lactose 1.25 mg in one ampoule of the first International Reference Preparation (1981). One *U.S.P.* parathyroid unit represents one-hundredth of the amount of Parathyroid Injection (*U.S.P.*) required to raise the calcium content of 100 mL of the blood serum of normal dogs 1 mg within 16 to 18 hours after administration. The first International Standard Preparation (1985) of parathyroid hormone, bovine, for *in vitro* bioassay consists of ampoules containing the lyophilised residue of about 10 µg of parathyroid hormone, bovine, in solution in 0.01 mol per litre acetic acid and 0.1% w/v mannitol buffer.

MRC and *U.S.P.* units are approximately equivalent to International units.

Adverse Effects and Precautions

Overdosage with parathyroid hormone causes hypercalcaemia (see under Calcium, Hypercalcaemia, p.1028).

Hypersensitivity reactions may occur, therefore skin tests for sensitisation should be carried out before intravenous administration.

Parathyroid hormone should be used with caution in patients with renal or cardiac disease.

Absorption and Fate

As parathyroid hormone is destroyed by proteolytic enzymes it is given by injection. Cleavage to peptide fragments occurs after administration, probably in the liver and kidney. Less than 1% of the parathyroid hormone is excreted in the urine.

Although the half-life of parathyroid hormone has been reported to be only a few minutes, the onset of action is slow. It has been stated that the response may last up to 36 hours.

Uses and Administration

Parathyroid hormone is involved in the maintenance of plasma-calcium concentrations through its actions on bone, kidney, and the gastro-intestinal tract. It increases bone resorption and stimulates production of 1,25-dihydroxycholecalciferol in the kidney. Renal excretion of inorganic phosphate is increased but overall that of calcium is decreased. It acts on the wall of the gut to increase absorption of calcium and phosphate and this is probably an indirect result of stimulating 1,25-dihydroxycholecalciferol production.

The response to an intravenous injection of parathyroid hormone may be used in the differential diagnosis of hypoparathyroidism and pseudo-hypoparathyroidism.

Parathyroid hormone was formerly used to raise the plasma-calcium concentration in acute hypoparathyroidism with tetany.

Synthetic preparations of the first 34 amino acids of human and bovine parathyroid hormones (PTH 1-34) are also in use, and other peptide fragments have been used investigationally.

Reviews of the actions of parathyroid hormone and its role in the regulation of plasma-calcium concentrations and of bone formation.— L. G. Raisz and B. E. Kream, *New Engl. J. Med.*, 1983, *309*, 29; I. Macintyre, *Br. med. Bull.*, 1986, *42*, 343.

A review of the management of parathyroid disorders in pregnancy.— Z. M. Van Der Spuy and H. S. Jacobs, *Postgrad. med. J.*, 1984, *60*, 245.

DIAGNOSIS OF PSEUDOHYPOPARATHYROIDISM. The absence of a phosphaturic response to the exogenous administration of parathyroid hormone has been used in the diagnosis of pseudohypoparathyroidism Type II. False positive responses have been described, however, and it was therefore suggested that the effect of parathyroid hormone on 1,25-dihydroxycholecalciferol concentrations should be measured in preference.— J. Thode and S. N. Holmegaard (letter), *New Engl. J. Med.*, 1983, *308*, 104. The response of 1,25-dihydroxycholecalciferol concentrations to parathyroid hormone in this condition has not been sufficiently demonstrated, and several indices of parathyroid hormone-responsiveness, including phosphaturia, calcaemia, and the rise in 1,25-dihydroxycholecalciferol should probably be measured.— A. M. Spiegel *et al.* (letter), *ibid.*

OSTEOPOROSIS. Twenty patients with severe vertebral crush fractures and one patient with a history of fractures of the long bones were given synthetic human parathyroid hormone fragment (PTH 1-34) as once-daily subcutaneous injections for 6 to 24 months. Calcium and phosphate balances improved in some patients but there was no significant improvement overall. There were, however, substantial increases in iliac trabecular bone volume and this new bone was histologically normal. It was suggested that as vertebrae are normally more than 75% composed of trabecular bone this hormone fragment might usefully increase the strength of the vertebrae in patients with axial osteoporosis.— J. Reeve *et al.*, *Br. med. J.*, 1980, *280*, 1340; *ibid.*, *281*, 191. See also J. Reeve *et al.*, *Lancet*, 1976, *1*, 1035.

Further references: J. Reeve *et al.*, *Bone*, 1986, *7*, 169 (PTH 1-34 and oestrogens); D. M. Slovik *et al.*, *J. Bone Mineral Res.*, 1986, *1*, 377 (PTH 1-34 and calcitriol).

Preparations

Parathyroid Injection (*U.S.P.*). A sterile solution in Water for Injections of the water-soluble hormone from the parathyroid glands of mammals, which has the property of increasing the calcium content of the b pH 2.5 to 3.5. It possesses a potency per mL of no than 100 *U.S.P.* parathyroid units.

Proprietary Names and Manufacturers

Parathorm (*Hormonchemie, Ger.*); Para-Thor-) (*Lilly, Austral.*; *Lilly, UK*).

8052-r

Calcitonin *(BAN, USAN, rINN).*

Thyrocalcitonin.

CAS — 9007-12-9.

A hormone, extracted from the mammalian t roid parafollicular cells and the ultimobranc gland in non-mammalian vertebrates, or obtai by synthesis, which has the property of lower the calcium content of blood. It is a polypept containing 32 amino acids. The amino-a sequence varies greatly from species to spec Forms used include: calcitonin (pork), calcito (salmon) or salcatonin, a synthetic human ca tonin, and a synthetic analogue of eel calcito (elcatonin).

8053-f

Calcitonin (Pork) *(BANM).*

CAS — 12321-44-7.

Pharmacopoeias. In *Br.* and *It.*

A polypeptide hormone extractable from po thyroid. It contains not less than 60 units per calculated with reference to the dried material.

A white or almost white powder. Soluble in wat and in solutions of alkali hydroxides; practical insoluble in acetone, alcohol, chloroform, a ether; sparingly soluble in solutions of miner acids. The *B.P.* states that it is prepared conditions designed to minimise microbial co tamination.

Store at a temperature not exceeding 25° in well-closed container. Protect from light. Unde these conditions it may be expected to retain i potency for not less than 2 years. Solutions fo injection should be used within 24 hours of pre paration or, if stored at 2° to 8°, within 7 days.

19126-n

Elcatonin *(rINN).*

CAS — 60731-46-6.

A synthetic analogue of eel calcitonin.

8054-d

Salcatonin *(BAN).*

Calcitonin (Salmon); SCT-1.

CAS — 47931-35-1.

Pharmacopoeias. In *Br.* and *Eur. Suppl.* Includes Human Calcitonin.

A polypeptide having the structure of salmon calcitonin I. It contains not less than 4000 units per mg calculated with reference to the peptide content.

A white or almost white, light powder. Freely soluble in water. Solutions are sterilised by filtration.

Store at 2° to 8° in a well-closed container. Protect from light. Under these conditions it may be expected to retain its potency for not less than 2 years.

Units

One unit of calcitonin, porcine, for bioassay is contained in approximately 10 µg of freeze-dried purified porcine calcitonin, with mannitol 5 mg in one ampoule of the first International Refer-

MARTINDALE

The Extra Pharmacopoeia

Thirtieth Edition

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Kathleen Parfitt

Assistant Editors
Anne V. Parsons
Sean C. Sweetman

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The first edition of the Extra Pharmacopoeia was published in July 1883. Squire's Companion was incorporated in the twenty-third edition in 1952. The twenty-ninth edition was published in January 1989. This current (thirtieth) edition was published in April 1993 and reprinted in September 1993

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Contents

Preface

Over the last 110 years the Extra Pharmacopoeia has developed through 30 editions from William Martindale's small pocketbook to this large volume. While the format has changed, the aim of what is now often known just as Martindale remains one of providing practising pharmacists and physicians with concise unbiased information on the substances used in medicine and pharmacy.

Successive early editions produced by William Martindale established the Extra Pharmacopoeia as a valuable and authoritative source of drug information. The book retained its clinical emphasis through the contributions of W. Wynn Westcott and its chemical and analytical content was developed especially under the editorship of Martindale's son, William Harrison Martindale. The Extra Pharmacopoeia continued to evolve after W.H. Martindale's death until the 25th edition, when it was subjected to a radical reshaping that increased its international coverage, removed the chemical and analytical data, and brought the book back to its early pharmaceutical and clinical roots.

That 25th edition provided a base from which the following 4 editions of Martindale evolved. However, with this 30th edition Martindale has been markedly changed yet again in order to meet the requirements of today's readership. These changes include a massive increase in information on proprietary medicines, a significant shift to a more clinical emphasis, an increase in the number of referenced reviews, and a shortening of the usual period between editions.

As with previous editions the monographs for all the drugs and substances in Martindale have been completely revised. In all there are 5132 monographs describing individual compounds or groups of related compounds. About 280 monographs were deleted from the last edition and about 620 have been added. The majority of the monographs have been grouped into 69 chapters that reflect the compounds' clinical or pharmaceutical use; this forms Part 1 of Martindale. Part 2 contains 832 monographs on drugs that do not readily fit into the chapters of Part 1, on some drugs under investigation, and on nondrug substances of interest to pharmacy and medicine.

The most obvious consequence of the changes that have been made for this edition is the increase in Martindale's size. This edition is 467 pages bigger than its predecessor and all of that increase is due to the enlarged and improved *international coverage of proprietary medicines*. Martindale is widely used to identify proprietary preparations. In the last edition a start was made to cover preparations containing more than one active ingredient and their proprietary names were listed under each monograph describing the relevant active ingredient. For this edition the coverage of mixed preparations has been widened and the information on each preparation has been presented in such a way that a reader can see at a glance what each contains. Lists of proprietary names still follow each monograph but details of each preparation are now included in a new Part 3 which extends to 481 pages and describes 46 000 preparations or groups of preparations from 14 countries including the *UK* and other European countries, North America, Australia, and South Africa; some preparations from Japan are also included. In addition Part 3 contains entries for official preparations from the *UK* and *USA*. For the proprietary preparations each entry provides the proprietary name, the manufacturer or distributor, the active ingredients, and a summary of that preparation's indications. The quantity of each active ingredient has not been included and dosage forms are only mentioned if different forms have the same proprietary name but different active ingredients. The inclusion of such information would have increased the number of entries inordinately. Also as Part 3 is intended to be used to identify preparations, usually from another country, such details would not necessarily be required for, if an alternative domestic preparation had to be supplied, the dose should be appropriate for that preparation and that patient.

Another development in this edition of Martindale is its increased clinical emphasis. Martindale is still a book of drug monographs but where possible the overall drug treatment of a particular condition has been drawn together and presented in one major referenced review or discussion. For example, the different treatments of migraine are reviewed on page 412 and cross-references to that review have been included in the monographs for the drugs discussed. This is something that will be developed in future editions.

The inclusion of references from major journals and other publications has been a feature of Martindale since its first edition. Useful data has been extracted from those publications and presented as individual abstracts. For some important topics in the 29th edition referenced reviews replaced what would normally have been series of individual abstracts. That practice has been considerably extended for this edition and wherever possible balanced reviews of the main publications have been written for the different topics described under each monograph. In all there are 11 300 reviews and abstracts and the total number of citations is 28 400.

A reference book like Martindale requires a comprehensive index. The index for this edition has been made up from 153 500 entries. It lists every drug name, synonym, code, chemical name, and preparation name or title. Where a substance is listed as an ingredient of one or more preparations in Part 3, the index entry for that substance is followed by a list of all its preparations. Diseases and conditions requiring treatment have also been indexed with page references to the major drugs used or to where treatment has been reviewed in detail. To help the reader locate the indexed information each index entry contains the relevant column number as well as the page number. The importance attached to the index is reflected in it occupying about one-sixth of the total number of pages of this edition.

The general plan since the 25th edition has been to produce a new and completely revised edition of Martindale about every 5 years. Sometimes the interval between editions has been longer, but not until this edition has that interval been reduced significantly. Thanks to the experience of the editorial staff and to modern technology this much enlarged 30th edition is published just over 4 years after the 29th edition to help satisfy the need for up-to-date information.

Martindale is based on published information. It is not a book of standards. Inclusion of a substance or a preparation is not to be considered as a recommendation for use, nor does it confer any status on the substance or preparation. Many of the monographs in Martindale are a page or more in length. Summaries have therefore been added to such monographs to provide readers with a brief overview. The inclusion of a summary does not mean that the drug being described is more important or more effective than one without a summary; all it means is that more words were required to describe its actions and uses. While considerable efforts have been made to check the material in Martindale, the publisher cannot accept any responsibility for errors and omissions. Also the reader is assumed to possess the necessary knowledge to interpret the information that Martindale provides.

Arrangement

PART 1 (pages 1–1327) contains 4300 monographs arranged in 69 chapters. These chapters generally bring together monographs on drugs and groups of drugs that have similar uses or actions. Cross-references are used to guide the reader to drugs that may be of interest in related chapters. Most chapters have an introduction which provides background information on that group of drugs. Some drugs such as the corticosteroids can be considered readily as a group with its members having many common actions; in such cases the introduction provides much of the information for that chapter. In chapters such as Antibacterial Agents or Antineoplastic Agents and Immunosuppressants the treatment of infections or malignant diseases, respectively, is discussed in detail in the introduction and information on the choice of drug(s) is given there.

PART 2 (pages 1329–1428) consists of a series of 832 short monographs arranged in the alphabetical order of their main titles. It includes monographs on some new drugs, on drugs not easily classified, and on drugs no longer used clinically but still of interest. There are also some monographs on toxic substances, the effects of which may require drug therapy.

PART 3 (pages 1429–1909) contains proprietary preparations from a range of countries as well as official preparations from the *UK* and *USA* from current editions of the *British Pharmacopoeia* and the *United States Pharmacopoeia* and *National Formulary*. Preparations from the *British Pharmaceutical Codex 1973* and earlier editions of the *British Pharmacopoeia* are included if still relevant and not covered by the current *British Pharmacopoeia*. The synonyms sometimes included for these preparations may be official synonyms or synonyms that are or have been in common use. For the proprietary preparations, the information provided includes the proprietary name, the manufacturer or distributor, the active ingredients, and a summary of the indications as given by the manufacturer.

Indexes

DIRECTORY OF MANUFACTURERS. In Martindale the names of manufacturers and distributors are abbreviated. Their full names are given in this directory together with the full address if it is available. This directory contains some 3500 entries.

GENERAL INDEX. To make fullest use of the contents of Martindale the general index should always be consulted. The exhaustive index to the drugs, preparations, compounds, pharmacological and therapeutic groups, and clinical uses in the book has been prepared from 153 500 individual index entries. As in previous editions, the index is arranged alphabetically 'word-by-word' rather than 'letter-by-letter'. The index indicates the column in which the relevant entry appears as well as the page.

Nomenclature

MARTINDALE IDENTITY NUMBERS. Each monograph title is followed by an identity number in brackets which consists of a maximum of 6 figures followed by a check character. These numbers are used in our computer manipulation and their purpose is to identify monographs in Martindale.

TITLES AND SYNONYMS. The title of each monograph is in English, with preference being given to British Approved Names, United States Adopted Names, and International Nonproprietary Names. These 3 authorities are now shown where appropriate. Names given as synonyms include commonly used abbreviated names; English, American, and Latin synonyms; names used in other languages when these may not be readily identifiable; manufacturers' code numbers; and chemical names. In some approved names it is now general policy to use 'f' for 'ph' in sulpha, 't' for 'th', and 'i' for 'y'; for this reason entries in alphabetical lists and indexes should be sought in alternative spellings if the expected spellings are not found. A table of contracted names for ions and groups used in approved names and titles is given on page xx.

CAS REGISTRY NUMBERS. Chemical Abstracts Service (CAS) registry numbers are provided, where available, for each monograph substance to help readers refer to other information systems. Numbers for various forms of the monograph substance are listed with the variation in form given in parenthesis.

Pharmacopoeias

The selected pharmacopoeias in which each substance appears are listed. Current copies of the pharmacopoeias and their addenda should be consulted for confirmation and for details of standards.

The pharmacopoeias covered include: *Austrian, Belgian,* Brazilian, *British, British Veterinary,* Chinese, Czechoslovakian, Egyptian, *European, French, German, Greek, Hungarian,* Indian, International, *Italian, Japanese, Mexican, Netherlands,* Nordic, *Portuguese,* Romanian, Russian, *Swiss,* Turkish, *United States* (including the *Formulary*), and Yugoslavian. Those *italicised* in the above list either appeared as new editions or were revised by supplements since the last edition of Martindale, and have been examined for this 30th edition.

The abbreviations for these pharmacopoeias are included in the list of abbreviations used in Martindale, see page xvi which also includes details of the edition and/or supplement(s) consulted.

Atomic and Molecular Weights

Atomic weights are based on the table of Atomic Weights as revised in 1983 by the Commission on *Atomic Weights and Isotopic Abundance*, International Union of Pure and Applied Chemistry and based on the ^{12}C scale (see page xxvi). Molecular weights are given corrected to one place of decimals or to four significant figures for relative weights of less than 100.

Pharmaceutical Information

Information on the chemical and physical properties of each substance is given when it is likely to be of use or interest, but only when it is certain that it applies to the form of substance being described in the monograph. Discrepancies in properties as described in the *B.P.* and *U.S.P.* are indicated.

PERCENTAGE STRENGTHS. Unless otherwise stated, solutions of solids in liquids are expressed as percentage w/v, of liquids in liquids as percentage v/v, and of *gases* in liquids as percentage w/w.

SOLUBILITY. The figures given for solubility in each monograph have generally been obtained from the major pharmacopoeias in which the substance is described, but should not be considered absolute. Unless otherwise indicated in the text, the figures are for solubility at 'ordinary room temperature' which is considered to be about 20°. Where solubilities are given in words, the following terms describe the indicated solubility ranges:

solubility	
very soluble	1 in less than 1
freely soluble	1 in 1 to 1 in 10
soluble	1 in 10 to 1 in 30
sparingly soluble	1 in 30 to 1 in 100
slightly soluble	1 in 100 to 1 in 1000
very slightly soluble	1 in 1000 to 1 in 10 000
practically insoluble	1 in more than 10 000

STORAGE. Substances and preparations should be stored under conditions which prevent contamination and diminish deterioration, and the conditions of storage given in the text indicate the precautions recommended in specific cases. Where authorities differ, we have included the most stringent storage requirement. The term 'a cool place' is generally used to describe a place in which the temperature does not exceed 15°. In general, the storage conditions apply to the monograph substance and not its solutions or preparations. Unless otherwise specified, all injections should be stored in alkali-free containers.

TEMPERATURE. Temperatures are expressed in degrees Celsius (centigrade) unless otherwise indicated.

Pharmacological and Therapeutic Information

Information on the adverse effects, treatment of adverse effects, precautions, absorption and fate, and uses and administration of each substance is provided by concise statements and these may be elaborated and expanded by referenced reviews and abstracts from papers and other publications.

This edition contains about 11 300 abstracts or reviews based on information in an ever widening range of publications. We have tried where possible to review the key papers. However, room has also been made for the interesting letter or case report where it is felt that information on a rare effect or action may be useful to the reader.

Much information has been found in sources such as World Health Organization publications, government reports and legislation, and other official and standard publications. Manufacturers' literature has been considered in the light of other available information.

The risks of administering drugs in pregnancy are well known and the

general principle is to give a drug only when the benefit to the individual mother outweighs the risk to the foetus. Where there is a clear risk it is noted under the Precautions or Adverse Effects heading but safety should not be inferred from the absence of a statement for any drug.

Interactions are described under the Precautions heading with detailed information being provided in the monograph for the drug that is being affected.

Doses

Doses are described under the Uses and Administration heading with as much detail as is necessary and available. Unless otherwise stated the doses represent the average range of quantities which are generally regarded as suitable for adults when administered by mouth. More information on doses and drug administration may be given in the abstracts or reviews. Unless otherwise specified, glucose injection is 5% w/v, sodium chloride injection is 0.9% w/v, and water is purified water.

When doses for children are expressed as a range of quantities within specified age limits, the lower dose applies at the lower age and the higher dose at the higher age.

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The Editor gratefully acknowledges the advice and assistance of the many experts who have suggested amendments to the text of Martindale. Thanks are due to M.J. Gilmour, M. Hooper, J.R. McKim, and especially to L.E. Ramsay for reading and commenting on drafts of this edition.

The Editor is grateful to the many organisations that have helped in providing information, including the World Health Organization, the British Pharmacopoeia Commission, and John Bell & Croydon.

Martindale staff have been able to call freely on the expertise of other members of the Royal Pharmaceutical Society's staff. In particular the Editor is grateful to A. Wade, the General Editor, A.B. Prasad and the editorial staff of the British National Formulary, and P.M. North and the staff of the library and information department.

Thanks are also due to B.J. Yates the Society's publisher and to J. Martin who assisted for some of the period of revision.

Many of the Martindale staff have worked on more than one edition and the Assistant Editors and Deputy Editor have worked with the Editor for the last 3 editions; that experience and the commitment from them and all the staff explain how we have been able to make the considerable developments with this new edition.

The contents of this 30th Edition were planned, written, checked, indexed, keyed, proofed, and processed by the Martindale staff. The Editor welcomes this opportunity to record his gratitude and appreciation of the dedicated services of the clerical staff, J.O. Byrne and D.D. Moore, and of the editorial staff: E.J. Aitchison, P.S. Blake, K. Eager, W.M. Farnsden, S.J. Futnell, S.L. Jefferson, J.M. McGlashan, G.C. Neathercoat, A. O'Rourke, S.J. Qureshi, and K.S. Riley. Finally, the Editor is indebted to the Assistant Editors, A.V. Parsons and S.C. Sweetman, and especially the Deputy Editor, K. Parfitt, for invaluable assistance and support.

London December 1992

there was a potent renal mechanism not inhibited by pamidronate. These results were confirmed by others.[11,12] Ralston *et al.*[11] speculated that the treatment of choice in ... would be ... pamidronate ... delayed for 24 to 48 hours combined therapy with pamidronate and calcitonin has been used and is considered by some workers to be the treatment of choice in severe hy- ... pamidronate ... pagetic resistant to therapy with corticosteroids plus calcitonin or calcitonin, corticosteroids, or pamidronate alone.

... 600 mg or eldronate 7.5 mg per kg body-weight daily by infusion for 3 consecutive days all reduced serum-calcium concentrations from those achieved by rehydration, but ... give as pamidronate in most hypercalcaemic patients; Ralston *et al.*[11] still preferred to use a single intravenous infusion of pamidronate.

... by mouth continued for 6 months after serum-alkaline phosphatase activity was back to normal or until urinary hydroxyproline excretion was back to normal or pamidronate ... daily by intravenous infusion for 10 days ...

... weekly or fortnightly intravenous infusion regimen which they claimed was successful. The regimen starts with a single intravenous infusion of pamidronate 30 mg in ... 250 mL of saline over 2 hours followed after one week ...

... A patient with Paget's disease refractory to human calcitonin has been reported to respond to treatment with disodium pamidronate 30 mg in 1000 mL of physiological ... infusion ...

... Paget's disease of bone. For a brief description of Paget's disease of bone and its treatment, see p.654.
Disodium pamidronate has been administered orally or intravenously (dosage ... to 600 mg) for maximum periods of 6 to 9 months.[1] Gastric intolerance was not a problem, possibly because the tablets were enteric-coated.
Others have preferred to use the intravenous route to ... Paget's disease, Casini *et al.*[6] give pamidronate by intravenous infusion in a dose of 15 mg daily for five consecutive days or weekly for 12 weeks. Both regimens were ... successful and well-tolerated. Herbert *et al.*[7] ...

... The first International Reference Preparative (1981) of parathyroid hormone, human, for immunoassay contains 0.1 unit in approximately 100 ng of freeze-dried purified ...

... cautionally been associated with the intravenous infusion of teriparatide acetate.

Uses and Administration

... of hypoparathyroidism and pseudohypoparathyroidism: a dose of 200 units is infused over 10 minutes. A 1-38 amino-acid fragment (hPTH 1-38) has also been used.
Teriparatide acetate has been given by subcutaneous injec- ... dogenous parathyroid hormone, whereas pseudohypoparathyroidism comprises a group of inherited disorders, characterised by resistance to the effects of parathyroid hormone. In pseudohypoparathyroidism type I ... both, in patients with the less common type II form of the disease, the urinary cyclic AMP, but not the phosphaturic, response to exogenous parathyroid hormone is normal. Teriparatide acetate is used diagnostically to distinguish ...

... drinking water and urinary concentrations of cyclic AMP and phosphate measured at standardised times before and after intravenous infusion of teriparatide acetate; measurements are ... fragment for diagnostic testing. *Ann Intern Med* 1988; 109: 800–4.
2. Ernst E, Knuth U. A simplified diagnostic test to hypoparathyroidism and pseudohypoparathyroidism type I ...

... injection for 6 to 24 months produced a ... increase in iliac trabecular bone volume. Calcium and phosphate balance improved in some patients but there was no ... improvement overall.[1] Slovik *et al.*[3] demon-

1. Thiébaud D, *et al.* Oral versus intravenous AHP,BP (APD) in the treatment of hypercalcemia of malignancy. *Bone* ...
2. Ralston SH, *et al.* Comparison of aminohydroxypropylidene diphosphonate, mithramycin, and corticosteroid/calcitonin in treatment of cancer-associated hypercalcaemia. *Lancet* 1985; ii: 907–10.
... aminohydroxypropylidene bisphosphonate (APD) for the hypercalcaemia of malignancy. *Br Med J* 1988; 296: 1464.
4. Ralston SH, Boyle IT. Treatment of hypercalcaemia of malignancy. *Br Med J* 1988; 296: 1464.
... *Lancet* 1988; ii: 617–18.
... hypercalcaemia with combined aminohydroxypropylidene diphosphonate and calcitonin. *Br Med J* 1988; 297: 1540–
... Ralston SH, *et al.* Comparison of three intravenous bisphosphonates in cancer-associated hypercalcaemia. *Lancet* 1989; ii: 1180–2.
... *Br Med J* 1988; 297: 973–6.
11. Ibe TT, *et al.* Treatment of hypercalcaemia in thyrotoxicosis with aminohydroxypropylidene diphosphonate. *Postgrad Med J* 1988; 64: 224–7.
... sis and a single infusion of 3-amino-1-hydroxypropylidene-1-bisphosphonate. *Arch Intern Med* 1990; 150: 2175–8.

5. Casini PA, *et al.* Low dose intravenous 3-amino-1-hydroxypropylidene-1,1-bisphosphonate (APD) for the treatment of Paget's disease of bone. *Ann Rheum Dis* 1986; 45: 1012–18.
6. Herbert HH, *et al.* Paget's disease of bone: early and late ... bone. *Br Med J* 1988; 296: 971.
7. Drake S, *et al.* Pamidronate sodium and calcitonin-resistant Paget's disease: immediate response in a patient. *Arch Intern Med* 1989; 149: 401–3.

Neridronic Acid (433-6)

Neridronic Acid (*rINN*).

CAS — [illegible].

Neridronic acid is used as a neridronate salt, a bisphosphonate with the general properties of disodium eldronate. It inhibits bone resorption and has been given by ... pamidronate in patients with Paget's disease of bone resistant to sodium eldronate. *Am J Med* 1987; 83: 276–82.

MARTINDALE

The ExtraPharmacopoeia

Thirty-first Edition

Edited by James E F Reynolds

Deputy Editor
Kathleen Parfitt

Assistant Editors
Anne V Parsons
Sean C Sweetman

Published by direction of the Council of the Royal Pharmaceutical Society of Great Britain and prepared in the Society's Publications Department

London
ROYAL PHARMACEUTICAL SOCIETY
1996

 Published by the Royal Pharmaceutical Society of Great Britain, 1 Lambeth High Street, London SE1 7JN, England.

The first edition of the Extra Pharmacopoeia was published in July 1883. Squire's Companion was incorporated in the twenty-third edition in 1952. The thirtieth edition was published in April 1993. This (thirty-first) edition was published in April 1996.

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Preface

The aim of Martindale, The Extra Pharmacopoeia is to provide practising pharmacists and physicians with unbiased evaluated information on drugs and medicines used throughout the world. Martindale therefore has to develop if it is to continue to meet that aim since the body of knowledge on existing drugs continues to grow, new drugs still emerge, new preparations are launched, old preparations abandoned, reformulated, or redefined, and the information needs of those practising pharmacy and medicine continue to evolve. The considerable changes that have been made with this edition are intended to meet those needs and we hope that they make the book easier to use.

All the monographs from the last edition have been revised, 173 having been deleted and 283 added, and reorganised into chapters that better reflect the uses of the drugs being described. For example, there is now one large chapter on Cardiovascular Agents rather than several chapters on groups such as Diuretics or Antihypertensive Agents. As a result, this edition contains 54 chapters in Part 1, fifteen fewer than in the 30th edition.

The most significant development, though, with this edition is the inclusion of a description of those diseases that are treated by drugs and a review of the choice of such treatment. Links are provided between the monographs and these reviews and *vice versa*. The reader can easily refer to a monograph from a disease review for further details about that drug. Conversely, reference can be made from a monograph to a disease review to see what other therapy may be used, although within each monograph we have tried to indicate that drug's place in the treatment of a disease or symptom for which it is indicated. This feature of the 31st edition of Martindale completes a development that was started in some chapters of the last edition.

The 30th edition was published 4 years after its predecessor to meet the need for more up-to-date information. That need is even more pressing today, hence the appearance of this edition 3 years after the 30th edition. For those who require even more up-to-date information from Martindale there are the electronic versions, sections of which are updated more frequently.

The information on preparations which is an important feature of Martindale has also been revised and the coverage of countries widened. Part 3 now describes 62 500 preparations or groups of preparations from 17 different countries. Within each preparation entry the individual ingredients have been indexed with the page numbers of the relevant drug monographs. In addition, entries in the General Index for single-ingredient preparations show the page numbers of the preparation entries in Part 3 as well as of the appropriate monographs.

Changes have been made to the typography to improve readability. Clearer headings have been introduced. Readers should welcome the increased type size in some sections as well as the adjustments to spacing which make the pages easier on the eye.

These developments have led to an increase in the size of Parts 1, 2, and 3. To compensate, and to keep the book in one volume, we have refined the index. We hope that the changes and reduction in size will make it easier to use without any loss of access to the edition's contents.

Martindale is based on published information and 26 300 selected references are included. Our aim is to cover the important studies and useful reviews and to place them in context. Mega studies and meta-analyses are playing a growing and important role in the study of drug treatment, and their findings and conclusions are considered in many of our chapters. However, there is also a place for the anecdotal report and the small study, and information from such sources is included where appropriate.

Martindale is not a book of standards. Inclusion of a substance or a preparation is not to be considered as a recommendation for use, nor does it confer any status on the substance or preparation. Many of the monographs in Martindale are a page or more in length. Summaries have therefore been added to such monographs to provide readers with a brief overview. The inclusion of a summary does not mean that the drug being described is more important or more effective than one without a summary; all it means is that more words were required to describe its actions and uses. While considerable efforts have been made to check the material in Martindale, the publisher cannot accept any responsibility for errors and omissions. Also the reader is assumed to possess the necessary knowledge to interpret the information that Martindale provides.

Arrangement

PART 1 (pages 1–1666) contains 4458 monographs arranged in 54 chapters. These chapters generally bring together monographs on drugs and groups of drugs that have similar uses or actions. Those chapters that describe drugs used in the management of disease contain descriptions of those diseases together with reviews of the choice of treatments and cross-references to the drugs discussed.

PART 2 (pages 1667–1768) consists of a series of 784 short monographs arranged in the alphabetical order of their main titles. It includes monographs on some new drugs, on drugs not easily classified, and on drugs no longer used clinically but still of interest. There are also some monographs on substances or techniques that may have a bearing on drug treatment such as bradykinin and gene therapy. Finally there are monographs on toxic substances, the effects of which may require drug therapy.

PART 3 (pages 1769–2395) contains proprietary preparations from a range of countries as well as official preparations from the *UK* and *USA* from current editions of the *British Pharmacopoeia* and the *United States Pharmacopoeia* and *National Formulary*. Preparations from the *British Pharmaceutical Codex 1973* and earlier editions of the *British Pharmacopoeia* are included if still relevant and not covered by the current *British Pharmacopoeia*. The synonyms sometimes included for these preparations may be official synonyms or synonyms that are or have been in common use. For the proprietary preparations, the information provided includes the proprietary name, the manufacturer or distributor, the active ingredients, and a summary of the indications as given by the manufacturer. We had hoped to include some information on those preparations manufactured within the hospital service, often known as 'hospital specials', and we are grateful to those hospitals who sent us data. Unfortunately there were some limitations on the amount of information that could be made public and the project had to be dropped.

Indexes

DIRECTORY OF MANUFACTURERS. In Martindale the names of manufacturers and distributors are abbreviated. Their full names are given in this directory together with the full address if it is available. This directory contains some 4800 entries.

GENERAL INDEX. To make fullest use of the contents of Martindale the general index should always be consulted. The exhaustive index to the drugs, preparations, compounds, pharmacological and therapeutic groups, and clinical uses in the book has been prepared from 131500 individual index entries. As in previous editions, the index is arranged alphabetically 'word-by-word' rather than 'letter-by-letter'. The index indicates the column in which the relevant entry appears as well as the page.

Nomenclature

MARTINDALE IDENTITY NUMBERS. Each monograph title is followed by an identity number in brackets which consists of a maximum of 6 figures followed by a check character. These numbers are used in our computer manipulation and their purpose is to identify monographs in Martindale.

TITLES AND SYNONYMS. The title of each monograph is in English, with preference being given to British Approved Names, United States Adopted Names, and International Nonproprietary Names. These 3 authorities are now shown where appropriate. Names given as synonyms include commonly used abbreviated names; English, American, and Latin

synonyms; names used in other languages when these may not be readily identifiable; manufacturers' code numbers; and chemical names. In some approved names it is now general policy to use 'f' for 'ph' in sulpha, 't' for 'th', and 'i' for 'y'; for this reason entries in alphabetical lists and indexes should be sought in alternative spellings if the expected spellings are not found. A table of contracted names for ions and groups used in approved names and titles is given on page xix.

CAS REGISTRY NUMBERS. Chemical Abstracts Service (CAS) registry numbers are provided, where available, for each monograph substance to help readers refer to other information systems. Numbers for various forms of the monograph substance are listed with the variation in form given in parenthesis.

Pharmacopoeias

The selected pharmacopoeias in which each substance appears are listed. Current copies of the pharmacopoeias and their addenda should be consulted for confirmation and for details of standards.

The pharmacopoeias covered include: *Austrian*, *Belgian*, *British*, *British Veterinary*, *Chinese*, *Czechoslovakian*, *European*, *French*, *German*, Hungarian, *International*, *Italian*, Japanese, *Netherlands*, *Portuguese*, *Swiss*, and *United States* (including the *Formulary*). Those *italicised* in the above list either appeared as new editions or were revised by supplements since the last edition of Martindale, and have been examined for this 31st edition.

The abbreviations for these pharmacopoeias are included in the list of abbreviations used in Martindale, see page xv which also includes details of the edition and/or supplement(s) consulted.

The standards of the European Pharmacopoeia take precedence over the standards of the national pharmacopoeias of those countries that are parties to the Convention on the Elaboration of a European Pharmacopoeia. These countries are currently Austria, Belgium, Bosnia-Herzegovina, Croatia, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Slovenia, Spain, Sweden, Switzerland, Turkey, the United Kingdom, and the Former Yugoslav Republic of Macedonia.

Atomic and Molecular Weights

Atomic weights are based on the table of Atomic Weights as revised in 1993 by the Commission on Atomic Weights and Isotopic Abundance, International Union of Pure and Applied Chemistry and based on the ^{12}C scale (see page xxi). Molecular weights are given corrected to one place of decimals or to four significant figures for relative weights of less than 100.

Pharmaceutical Information

Information on the chemical and physical properties of each substance is given when it is likely to be of use or interest, but only when it is certain that it applies to the form of substance being described in the monograph. Discrepancies in properties as described in the BP and USP are indicated.

PERCENTAGE STRENGTHS. Unless otherwise stated, solutions of solids in liquids are expressed as percentage w/v, of liquids in liquids as percentage v/v, and of gases in liquids as percentage w/w.

SOLUBILITY. The figures given for solubility in each monograph have generally been obtained from the major pharmacopoeias in which the substance is described, but should not be considered absolute. Unless otherwise indicated in the text, the figures are for solubility at temperatures between 15° and 25°. The information usually relates to w/v solubilities but in some cases is v/v if the monograph substance itself is a liquid. Where solubilities are given in words, the following terms describe the indicated solubility ranges:

solubility	
very soluble	1 in less than 1
freely soluble	1 in 1 to 1 in 10
soluble	1 in 10 to 1 in 30
sparingly soluble	1 in 30 to 1 in 100
slightly soluble	1 in 100 to 1 in 1000
very slightly soluble	1 in 1000 to 1 in 10 000
practically insoluble	1 in more than 10 000

STORAGE. Substances and preparations should be stored under conditions which prevent contamination and diminish deterioration, and the conditions of storage given in the text indicate the precautions recommended in specific cases. Where authorities differ, we have included the most stringent storage requirement. The term 'a cool place' is generally used to describe a place in which the temperature is between 8° and 15°. In general, the storage conditions apply to the monograph substance and not its solutions or preparations.

TEMPERATURE. Temperatures are expressed in degrees Celsius (centigrade) unless otherwise indicated.

Pharmacological and Therapeutic Information

Information on the adverse effects, treatment of adverse effects, precautions, pharmacokinetics, and uses and administration of each substance is provided by concise statements and these may be elaborated and expanded by referenced reviews and abstracts from papers and other publications.

This edition contains about 11 600 abstracts or reviews based on information in an ever widening range of publications. We have tried where possible to review the key papers. However, room has also been made for the interesting letter or case report where it is felt that information on a rare effect or action may be useful to the reader.

Much information has been found in sources such as World Health Organization publications, government reports and legislation, and other official and standard publications. Manufacturers' literature has been considered in the light of other available information.

The risks of administering drugs in pregnancy are well known and the general principle is to give a drug only when the benefit to the individual mother outweighs the risk to the foetus. Where there is a clear risk it is noted under the Precautions or Adverse Effects heading but safety should not be inferred from the absence of a statement for any drug.

Interactions are described under the Precautions heading with detailed information being provided in the monograph for the drug that is being affected.

Doses

Doses are described under the Uses and Administration heading with as much detail as is necessary and available. Unless otherwise stated the doses represent the average range of quantities which are generally regarded as suitable for adults when administered by mouth. More information on doses and drug administration may be given in the abstracts or reviews. Unless otherwise specified, glucose injection is 5% w/v, sodium chloride injection is 0.9% w/v, and water is purified water.

When doses for children are expressed as a range of quantities within specified age limits, the lower dose applies at the lower age and the higher dose at the higher age.

Acknowledgements

The Editor gratefully acknowledges the advice and assistance of the many experts who have suggested amendments to the text of Martindale. Thanks are due to DN Bateman, P Bennett, MJ Brodie, PR Jackson, T Pullar, LE Ramsay, CJC Roberts, M Summerhayes, and WW Yeo for reading and commenting on drafts of this edition.

The Editor is grateful to the many organisations that have helped in providing information, including the World Health Organization and the British Pharmacopoeia Commission.

Martindale staff have been able to call freely on the expertise of other members of the Royal Pharmaceutical Society's staff. In particular the Editor is grateful to A Wade, the General Editor, AB Prasad and the editorial staff of the British National Formulary, and the staff of the library and information department. Thanks are also due to S Dutton and K Rowan.

Almost all of the Martindale staff have worked on more than one edition and many have worked with the Editor for the last 3 or 4 editions; that experience and the commitment from them and all the staff explain how we have once again been able to make the considerable development to Martindale.

The contents of this 31st edition were planned, written, checked, indexed, keyed, proofed, and processed by the Martindale staff. The Editor welcomes this opportunity to record his gratitude to all the staff: to Claire Ryan for clerical assistance; to the editorial staff Kathleen Eager, Susan Funnell, Prakash Gotecha, Susan Handy, Susan Jefferson, Eileen Laughton, Gail Neathercoat, Keith Riley, and Paul Weller for their much appreciated assistance; to Paul Blake, Julie McGlashan, and the Assistant Editors, Anne Parsons and Sean Sweetman, who contributed significantly to the implementation of the plans for this edition; and to the Deputy Editor, Kathleen Parfitt, for invaluable support and advice.

London January 1996

Uses and Administration continued

1. Eggelmeijer F, *et al.* Clinical and biochemical response to single infusion of pamidronate in patients with active rheumatoid arthritis: a double blind placebo controlled study. *J Rheumatol* 1994; 21: 2016–20.
2. Maccagno A, *et al.* Double blind radiological assessment of continuous oral pamidronic acid in patients with rheumatoid arthritis. *Scand J Rheumatol* 1994; 23: 211–14.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations
Aust.: Aredia; *Austral.:* Aredia; *Belg.:* Aredia; *Canad.:* Aredia; *Fr.:* Arédia; *Ital.:* Aredia; *Neth.:* Aredia; *Norw.:* Aredia; *SAfr.:* Aredia; *Swed.:* Aredia; *Switz.:* Arédia; *UK:* Aredia; *USA:* Aredia.

Neridronic Acid (9534-e)

Neridronic Acid (*rINN*).
AHDP; AHHxBP; Aminohexane Diphosphonate; (6-Amino-1-hydroxyhexylidene)diphosphonic acid.
$C_6H_{17}NO_7P_2$ = 277.2.
CAS — 79778-41-9.

Neridronic acid is used as a neridronate salt, a bisphosphonate with the general properties of disodium etidronate (see p.779). It inhibits bone resorption and has been given intravenously or by mouth in the treatment of malignant hypercalcaemia and diseases associated with excessive bone turnover such as Paget's disease of bone.

Bisphosphonates are widely used in the treatment of Paget's disease of bone, see p.775, and of hypercalcaemia, see p.1170. In the management of osteoporosis they may be employed as second-line therapy, see p.773.

References to the use of neridronate are given below.

1. Delmas PD, *et al.* Beneficial effects of aminohexane diphosphonate in patients with Paget's disease of bone resistant to sodium etidronate. *Am J Med* 1987; 83: 276–82.
2. O'Rourke NP, *et al.* Treatment of malignant hypercalcaemia with aminohexane bisphosphonate (neridronate). *Br J Cancer* 1994; 69: 914–17.

Parathyroid Hormone (9051-e)

Parathyrin; PTH.
CAS — 9002-64-6.

Parathyroid hormone is a single-chain polypeptide isolated from the parathyroid glands. It contains 84 amino acids and in man the first 34 appear to be responsible for the hormonal activity. The amino-acid sequence varies according to the source.

Endogenous parathyroid hormone is involved in the maintenance of plasma-calcium concentrations having a hypercalcaemic effect through its actions on bone, kidney, and indirectly on the gastro-intestinal tract (see also under Parathyroid Disorders, p.776).

Exogenous parathyroid hormone was formerly used in acute hypoparathyroidism with tetany. It has also been used in the differential diagnosis of hypoparathyroidism and pseudohypoparathyroidism.

Synthetic preparations of the first 34 amino acids of human and bovine parathyroid hormones (PTH 1-34) are now used for diagnostic purposes, see Teriparatide Acetate, p.782.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations
UK: Para-Thor-Moset.

Risedronic Acid (10591-d)

Risedronic Acid (*rINN*).
NE-58095. [1-Hydroxy-2-(3-pyridinyl)ethylidene]diphosphonic acid.
$C_7H_{11}NO_7P_2$ = 283.1.
CAS — 105462-24-6 (*risedronic acid*); 115436-72-1 (*risedronate sodium*).

NOTE. Risedronate Sodium is *USAN*.

Risedronic acid is under investigation as a risedronate salt, a bisphosphonate with the general properties of disodium etidronate (see p.779). It inhibits bone resorption and has been tried by mouth and parenterally in the treatment of diseases associated with excessive bone turnover.

Teriparatide Acetate (12640-e)

Teriparatide Acetate (*USAN, rINNM*).
hPTH 1-34 (teriparatide).
$C_{181}H_{291}N_{55}O_{51}S_2.xH_2O.yC_2H_4O_2$.
CAS — 52232-67-4 (*teriparatide*); 99294-94-7 (*teriparatide acetate*).

Units

The potency of teriparatide acetate is expressed in terms of units of human parathyroid hormone activity.

The first International Reference Preparation (1981) of parathyroid hormone, human, for immunoassay contains 0.1 unit in approximately 100 ng of freeze-dried purified hormone.

Adverse Effects

Gastro-intestinal disturbances, a metallic taste, tingling of the extremities, and pain at the site of injection have occasionally been associated with the intravenous infusion of teriparatide acetate.

Uses and Administration

Teriparatide is a synthetic polypeptide that consists of the 1-34 amino-acid fragment of human parathyroid hormone, the biologically active N-terminal region. The acetate is given by intravenous infusion in the differential diagnosis of hypoparathyroidism and pseudohypoparathyroidism; a dose of 200 units is infused over 10 minutes.

Diagnostic use. In hypoparathyroidism, hypocalcaemia a hyperphosphataemia result from a deficiency in endogenous parathyroid hormone, whereas pseudohypoparathyroidism characterised by resistance to the effects of parathyroid hormone (see Parathyroid Disorders, p.776).

Teriparatide acetate is used diagnostically to distinguish between hypoparathyroidism and pseudohypoparathyroidism types I and II.[1] A synthetic 1-38 fragment of human parathyroid hormone (1-38 hPTH) has also been used diagnostically.

1. Mallette LE. Synthetic human parathyroid hormone 1-34 fragment for diagnostic testing. *Ann Intern Med* 1988; 108: 830–4.
2. Kruse K, Kracht U. A simplified diagnostic test in hypoparathyroidism and pseudohypoparathyroidism type I with synthetic 1-38 fragment of human parathyroid hormone. *Eur J Pediatr* 1987; 146: 373–7.

Osteoporosis. Teriparatide, administered as daily subcutaneous injections, is being investigated in the treatment of osteoporosis which is discussed on p.773.

References to the use of parathyroid hormone fragments in osteoporosis are given below.

1. Slovik D, *et al.* Restoration of spinal bone in osteoporotic men by treatment with human parathyroid hormone (1-34) and 1,25-dihydroxyvitamin D. *J Bone Miner Res* 1986; 1: 377–81.
2. Ettinger EP, *et al.* Increase of vertebral density in osteoporotic combination therapy with 1-38 hPTH and calcitonin nasal spray. *Acta Endocrinol (Copenh)* 1988; 117 (suppl 297): 167–8.
3. Reeve J, *et al.* Treatment of osteoporosis with human parathyroid peptide and observations on effect of sodium fluoride. *Br Med J* 1980; 281: 314–18. Correction. *ibid.*: 477.
4. Finkelstein JS, *et al.* Parathyroid hormone for the prevention of bone loss induced by estrogen deficiency. *N Engl J Med* 1994; 331: 1618–23.

Preparations

Names of preparations are listed below; details are given in Part 3.

Proprietary Preparations
USA: Parathar.

Tiludronic Acid (10481-e)

Tiludronic Acid (*BAN, rINN*).
SR-41319. [[(p-Chlorophenyl)thio]methylene]diphosphonic acid.
$C_7H_7ClO_6P_2S$ = 318.6.
CAS — 89987-06-4.

NOTE. Tiludronate Disodium is *USAN*.

Tiludronic acid is used as a tiludronate salt, a bisphosphonate with the general properties of disodium etidronate (see p.779). It inhibits bone resorption and has been given by mouth in the treatment of diseases associated with excessive bone turnover such as Paget's disease of bone and osteoporosis.

For the role of bisphosphonates in the treatment of Paget's disease of bone see p.775, and for the management of osteoporosis see p.773. References to the use of tiludronate are given below.

1. Adami M, *et al.* Treatment of Paget's disease of bone with [4-chloro-phenylthiomethylene bisphosphonate. *Clin Rheumatol* 1989; 8: 71–8.
2. Reginster JY, *et al.* Prevention of postmenopausal bone loss by tiludronate. *Lancet* 1989; ii: 1469–71.
3. Reginster JY, *et al.* Paget's disease of bone treated with a 3-day course of oral tiludronate. *Ann Rheum Dis* 1992; 51: 36–

AFFIDAVIT OF SERVICE

United States Court of Appeals
for the Federal Circuit
No. 05-1184
----------)

IN RE MARTIN BILLGER and MIKAEL BRULLS

----------)

I, John C. Kruesi, Jr., being duly sworn according to law and being over the age of 18, upon my oath depose and say that:

I am retained by Foley & Lardner LLP, attorneys for Appellants.

That on the **15th Day of March 2005**, I served the within **Brief of Appellants Martin Billger & Mikael Brulls** upon:

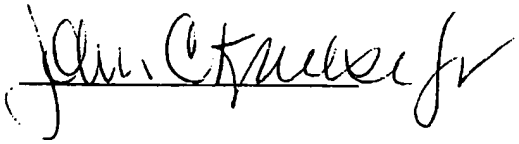
JOHN M. WHEALAN
LINDA M. ISACSON
HEATHER F. AUYANG
OFFICE OF THE SOLICITOR
P.O. Box 15667
Arlington, VA 22215
(571) 272-9035

Attorneys for Appellee

via Express Mail, by depositing 2 true copies of each, enclosed in a properly addressed wrapper, in an official depository of the USPS.

Unless otherwise noted, 12 copies have been hand-delivered to the Court on the same date as above.

March 15, 2005



AFFIDAVIT OF SERVICE

United States Court of Appeals
for the Federal Circuit
No. 05-1184
----------)

IN RE MARTIN BILLGER and MIKAEL BRULLS

----------)

I, John C. Kruesi, Jr., being duly sworn according to law and being over the age of 18, upon my oath depose and say that:

I am retained by Foley & Lardner LLP, attorneys for Appellants.

That on the **22nd Day of March 2005**, I served the within **Corrected Brief of Appellants Martin Billger & Mikael Brulls** upon:

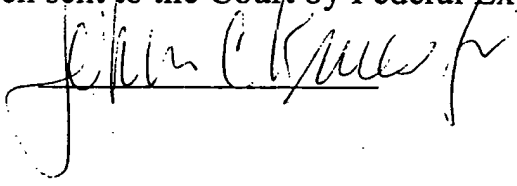
JOHN M. WHEALAN
LINDA M. ISACSON
HEATHER F. AUYANG
OFFICE OF THE SOLICITOR
P.O. Box 15667
Arlington, VA 22215
(571) 272-9035

Attorneys for Appellee

via Express Mail, by depositing 2 true copies of each, enclosed in a properly addressed wrapper, in an official depository of the USPS.

Unless otherwise noted, 12 copies have been sent to the Court by Federal Express.

March 22, 2005



FORM 19. Certificate of Compliance With Rule 32(a)

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION, TYPEFACE REQUIREMENTS, AND TYPE STYLE REQUIREMENTS

1. This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B).

☒ The brief contains 10, 199 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii), or

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☒ The brief has been prepared in a proportionally spaced typeface using MS Word *(word processing program)* in 14 point, Times New Roman font *(size and name of type style)*, or

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(s) Courtney C. Bruckhoff

(Name of Attorney)

Attorney for Appellants

(State whether representing appellant, appellee, etc.)

March 15, 2005

(Date)